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The Dynamic Assessment of Cardiac Repolarisation in Health and Disease

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Abstract:

The QT interval, as measured on the electrocardiogram, is a reflection of the duration of cardiac electrical depolarisation and repolarisatio. Prolongation of this interval has long been recognised to be associated with an increased risk of cardiac arrhythmias.

This thesis discusses the history of measurement of cardiac repolarisation (the QT interval), and subsequently the various methods to correct QT for heart rate. After highlighting the limitations of traditional QT correction formulae, I go on to describe a novel method for continuous automated measurement the relationship between QT and heart rate from ambulatory ECG recordings. This method's reproducibility and the effect of lead selection is then established in healthy volunteers.

As cardiac repolarisation and the QT interval is known to be abnormally prolonged in certain cardiac diseases, and that QT prolongation can precipitate malignant arrhythmias, the second section of the thesis assesses the repolarisation characteristics of patient groups with heart failure and hypertrophic cardiomyopathy. The repolarisation properties are then compared to measures of disease severity, and traditional markers for sudden death in these patients.

The third section of the thesis presents data gathered from patients with implantable cardiac defibrillators (ICDs), with three main goals: firstly to establish whether there is a particular time of day that these patients are prone to arrhythmias; secondly to establish whether there are particular abnormalities of the repolarisation characteristics in these patients at that time of day; and thirdly to establish whether overall 24h repolarisation properties convey any prognostic information with regards to the risk of further malignant ventricular arrhythmias.

The results demonstrate that the method employed throughout the thesis is reproducible in healthy volunteers. In addition, I show that in patients with heart failure and hypertrophic cardiomyopathy, there are marked abnormalities in several parameters of cardiac repolarisation, and that these abnormalities are progressive with the severity of the disease. These abnormalities might be expected to confer an increased risk of sudden arrhythmic death. I also show that sustained ventricular arrhythmias are far more common in the early hours of the morning in patients with a history of malignant ventricular arrhythmias, and that an increase in sympathetic activity at that time of day appears to be responsible for this. There are simulatneous changes in cardiac repolarisation, which are less marked in subjects on beta blockade. Previous authors have suggested that an abnormally increased 'rate corrected QT' may be important in the early morning 'high risk' period, but from describing the overall QT/heart rate characteristic in more detail with the method employed, I have demonstrated that the repolarisation characteristic during the high risk period is that of a ***shortened*** QT.

In conclusion, this thesis has exposed new information about the complexities of cardiac repolarisation and its measurement in both health and disease. Some doubt is cast over existing methodologies for QT 'correction' and some of the conclusions based on these methods.

"I don't want to achieve immortality through my work. I want to achieve it through not dying".

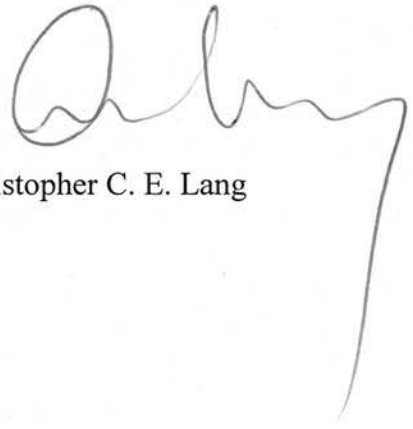
Woody Allen

Contents

Declaration

This thesis describes research undertaken at the University of Edinburgh Cardiovascular Research Unit and the Department of Cardiology, Royal Infirmary of Edinburgh, during the period January 1999- January 2003. I undertook this research as a Junior Research Fellow, funded entirely by the British Heart Foundation. I have had invaluable help from friends and colleagues, and collaborations have existed which have been formally acknowledged in the text. Otherwise, the work in this thesis is my own, and the writing of the substance of the text has been entirely my own undertaking. Some of the work discussed in this thesis has been published in academic journals. This work is cited in the appendix.

This thesis has not been submitted, neither whole nor in part, for any other degree, diploma or other qualification.



Christopher C. E. Lang

Acknowledgements

I am indebted to many people, without whom this work could not have taken place. Firstly, I have to thank the British Heart Foundation and their volunteers for having provided the financial support for me. I hope that the publications arising from this work will provide reassurance that their funding was invested wisely.

I am also grateful to my friend, colleague and collaborator, Sam Mohiddin, currently working at the NIH in Bethesda. He provided me with valuable data on patients with hypertrophic cardiomyopathy, recruited by himself and Dr Fananapazir's group. Dr Fananapazir, an authority in the field of hypertrophic cardiomyopathy, has also provided his support and encouragement to assist our research. I hope that our collaborations will continue to grow.

I am fortunate to have worked on both the East and West of Scotland during my training, and were it not for this, it would have been more difficult to organise the collaboration between Glasgow Royal Infirmary and the Royal Infirmary of Edinburgh. The defibrillator study was designed to be a large study, and were it not for the assistance of Professor Cobbe and the support of Dr Rae and Dr Rankin in Glasgow, the study would not have got off the ground. I must also give special mention to the pacing technicians in both Edinburgh and Glasgow who patiently taught me a great deal about defibrillators and introduced me to all the patients in the study.

I am fortunate to have been working in the cardiology department in the Royal Infirmary of Edinburgh. A department renowned for its friendly and supportive staff, at all levels through doctors, technicians, nurses and administrative staff. I have always felt welcome, and have always been encouraged and assisted wherever possible.

My supervisors, Dr Flapan and Dr Neilson, have consistently provided me with technical, clinical, financial and moral support. Their contrasting styles have taught me a great deal and I have grown from the experience in many ways. I would like to thank them for their patience and advice.

The patients involved in these studies are arguably the most important individuals. Were it not for their altruistic willingness to help, none of this work would have been possible. I hope that this research may, in some way, help them and others in the future.

On a personal level, I have to dedicate this work to two people in particular. Firstly to Dr Hugh Miller. Although I could never aspire to match his abilities and wisdom as a clinician and teacher, I am certain that were it not for his influence upon me from my days as a medical student and throughout my clinical training, I would never have pursued a career in cardiology and have such an interest in arrhythmias.
Secondly, my wife Pina, who has helped me through the difficult times, and shares the successes. I could not have done it without her.

Foreword

My interest in the QT interval originates from my elective period of study at Medical School, which I was fortunate enough to spend in the 'Ospedale Maggiore di Milano, Dipartimento di Fisiologia Clinica e Ipertensione' under the supervision of Professor Peter Schwartz, Dr Silvia Priori and Dr Carlo Napolitano. These researchers have been at the forefront of research into the congenital long QT syndromes for many years. While there, I studied the effects of the pure class III anti-arrhythmic agent d-sotalol and its effects on action potential duration in isolated guinea pig myocytes. I was fascinated by the phenomenon of early after-depolarisations which are seen when the action potential becomes excessively prolonged. This is thought to be the trigger for the development of Torsades des Pointes in patients with prolonged QT. Since then I have always taken an interest in arrhythmias, particularly those that are related to the QT interval.

In 1998 I contacted Dr James Neilson in the department of medical physics at the Royal Infirmary of Edinburgh. He had been developing a novel method to analyse the QT-heart rate relationship from Holter recordings. After discussion with him about the method and seeing a demonstration of it in action, I realised that it was something that held great promise as it used a new and ingenious approach to the analysis of dynamic QT interval analysis. Following this Dr Neilson and I wrote a grant application with Dr Flapan to the British Heart Foundation to evaluate the method in clinical settings. I was successful in receiving a 2 year fellowship grant.

The first section of the thesis concentrates on the history of the QT interval, factors that influence it, and methods currently employed to assess rate independent changes in QT. I go on to examine the ability of the method to monitor short and long term changes in the QT/RR relationship in health and disease. The latter part of the thesis is concerned with a study of patients with prior history of malignant arrhythmias who have received implantable defibrillators, the goal being to establish whether QT/RR parameters can yield further insights into the initiation and maintenance of malignant ventricular arrhythmias.

The scope of my research was involved principally with the temporal relationship between the QT interval and heart rate. As the recordings obtained for this research were from 2 channel Holter recorders, little comment can be made about the spatial dispersion of repolarisation. Interest in the measurement of QT dispersion was rekindled by the late Professor Campbell as a potentially useful tool in the risk stratification of patients at risk from malignant arrhythmias. Since the early papers on this subject, numerous articles have been published in a broad range of patient populations. As with every test, there always exist backers and sceptics. One of the issues with QT dispersion (QTd) is the potentially large errors in measurement. These errors have been reduced somewhat by the introduction of automated measurement of QTd. Nonetheless, the controversy and debate continues, with some authors referring to it as "the greatest fallacy in electrocardiography in the '90s" (Rautaharju 1999). While there is no doubt that spatial dispersion in repolarisation can provide a substrate for the development of re-entrant circuits, it has been said that QT

dispersion from 12 lead ECGs should not be thought of as the gold standard. Recently, some researchers have shown that the measured QT dispersion seems to be a reflection of the geometrical projection of the T wave on the surface ECG, and have questioned its significance in disease states (Kors, van Herpen and Van Bemmel 1999). While useful information about arrhythmic risk may well come from QTd, we will not discuss it further in the context of this thesis.

Glossary of Terms

α – Alpha is used to refer to the proportion of total QT adaptation to a given change in heart rate that occurs rapidly (within one to two beats). Generally this is in the region of 20-30% of total adaptation. The remainder (1-α) occurs gradually, and requires several minutes to reach a steady state.

Bazett's QT correction Formula – $QTc = QT/\sqrt{RR}$, which can also be written as $QT/RR^{0.5}$, with time intervals in seconds.

Correlation coefficient (r) – During QT analysis of Holter recordings, the analysed will continuously 'best-fit' the lag compensated QT and RR' data against an exponential curve with variables QTo and J. To ensure that the lag compensation is correctly adjusted, the correlation coefficient is continuously calculated. If the correlation between QT and RR' data and an exponential curve falls below 0.8, this section of data is excluded from calculation of the 24h mean values of QTo and J.

CL – Cycle length. The cycle length is the period between two successive electrograms. This is generally reserved for discussion of intracardiac electrograms, but can also be used for surface recordings. For example, the RR interval and ventricular cycle length refer to the same thing.

Error correction – Prior to running the QT analysis programme, electrogram recordings are automatically edited to exclude noisy segments or segments with very

frequent ectopic beats that would introduce errors into the calculations. Recordings were not analysed if greater that 20% error correction was required.

Fridericia's QT correction Formula – $QTc = QT/\sqrt[3]{RR}$, which can also be written as $QT/RR^{0.333}$, with time intervals in seconds.

J – Throughout the thesis, we model the QT/RR relationship to a general exponential formula, which is expressed as $QT = QTo.\ RR^{J}$, with an X and Y intercept at 0,0. The repolarisation characteristics (or QT/RR relationship) can be expressed as a curve at any point in time by knowing the two variables QTo and J. J is used to denote the variable exponent, and does not have units. During analysis of Holter recordings, J is continuously calculated from a 5 minute window of data, which scrolls through the entire recording. Throughout most of the thesis, the 24h mean value is expressed, but instantaneous values can also be quoted.

QT adaptation lag – The QT interval is sensitive to changes in heart rate. However, the relationship between changes in rate and changes in QT is complex, with a fast component that is effectively instantaneous (within one beat), and a second component which takes several minutes to reach a steady state. This delay in adaptation is referred to as QT adaptation lag' throughout the thesis.

QT – The QT interval is measured on electrocardiograms from the onset of the Q wave to the offset (or end) of the T wave.

QTc – The heart rate 'corrected' QT interval. As there are several formulae to correct the QT interval for heart rate, it is usual to state which formula is being employed. The most common and widely accepted is Bazett's formula ($QTc=QT/\sqrt{RR}$).

QTd – QT dispersion, which is calculated as the difference between the longest and shortest QT intervals on a standard 12 lead ECG. It is felt to probably reflect heterogeneity of cardiac repolarisation and has been associated with an increased risk of death in some conditions.

QT Hysteresis – If consecutive QT intervals are plotted against preceding RR intervals, as heart rate changes the QT interval will adapt to the changes in heart rate. However, due to the aforementioned 'lag' in adaptation, the plot will consist of loops created by accelerations and decelerations in heart rate, with QT lagging behind.

QTo – This describes the Y axis value at an X-axis ordinate of RRo on a calculated QT/RR curve which by convention is chosen as 1000ms. It can be considered the equivalent to QTc. As the relationship between QT and RR varies independently of heart rate, it is not sufficient to quote QTo to describe an individuals repolarisation characteristics. This is discussed in the text.

RR – The time interval between two successive QRS complexes on an ECG. By convention this should be measured from the peak of the R wave to the next R wave.

RR' – This refers to RR interval data from Holter recordings to which a delay has been applied in order to temporally 'align' the continuously changing QT intervals with the RR intervals that have brought about the change in QT ('lag compensated' RR intervals). This is necessary in order to compensate for the phenomenon of QT adaptation lag.

SD of J – Throughout the day, the QT/RR relationship varies. Normally this is around fairly constant mean values of QTo and J. In order to express the degree of variation in the relationship, the standard deviation of J is calculated by calculating the standard deviation of the continuously calculated values of J from the 24h recording.

Slope (S) – Slope is used in this work to describe the tangent to a point on the QT/RR curve. During the process of analysing QT and RR data, QT data is compared with 'lag compensated' RR data (RR', see above). By plotting consecutive QT and RR pairs, it is possible to measure the slope of these points. As the QT/RR relationship is not linear but curved over the physiological range of heart rates, slope cannot be used to describe the overall relationship. Therefore, slope is used, along with QT and RR, to calculate the 'best-fitting' exponential curve, expressed as $QT=QTo.RR^{J}$. Slope does not have units.

τ – Tau is used to refer to the time constant of the delayed component of QT adaptation.

Chapter 1

Introduction to cardiac action potentials and the QT interval

1.1 Introduction

The cardiac action potential (AP) is responsible for the spontaneous cardiac rhythm which keeps the heart beating. In the sino-atrial node (SAN), pacemaker cells exhibit a diastolic outward current that results in spontaneous depolarisation once a threshold has been reached. The rate at which the SAN cells depolarise in diastole is determined by autonomic tone and mechano-electrical feedback.

The AV node also displays automaticity, albeit at a slower rate, hence sinus rhythm dominates under normal circumstances. The specialised conduction tissues of the His-Purkinje system conduct impulses throughout both ventricles rapidly to produce a co-ordinated contraction of the muscular chambers with ejection of blood to the lungs and body. In ventricular myocytes, the action potential is of longer duration than the cells of the conduction system and it is during the plateau phase of the action potential that the myocyte, and hence the heart, contracts.

1.1.1 Generation of the Ventricular Action Potential

The ventricular action potential as shown in figure 1 is composed of four phases. Phase 0 is the rapid upstroke, due primarily to opening of voltage dependent sodium channels, with influx of positively charged sodium ions and a net depolarisation of the cell. Phase 1 is the sharp downward notch. Phase 2 is the plateau phase which prolongs the action potential, during which there is an efflux of potassium ions with net repolarisation of the cell. During this phase there is also an influx of calcium ions, with release of stored calcium from the sarcoplasmic reticulum (SR) (counteracting

the repolarising currents) that enables contraction of the myocyte. Phase 3 is termed delayed repolarisation and ends when the resting membrane potential has been achieved. Phase 4 often starts from a point of hyper-polarisation whereby the membrane potential is more negative than baseline and this renders the cell less excitable. The timing of the various currents involved are shown in Figure 1.

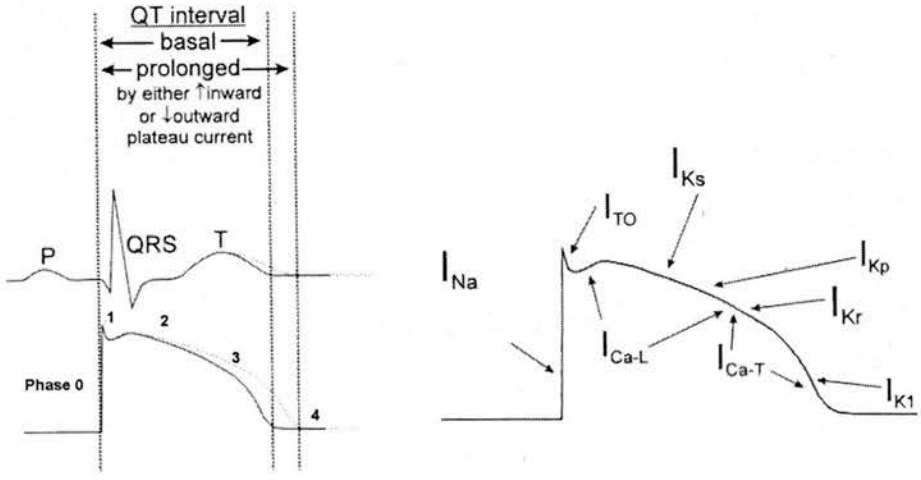


Figure 1.1 : The action potential and QT interval are aligned in the left panel to demonstrate the relationship between the surface ECG and the AP. The right panel indicates the various currents active in the different phases of the action potential. The QRS complex is a reflection of ventricular myocytes depolarisation caused by the rapid influx of sodium ions. During the ST segment of the ECG, most myocytes are in the plateau phase of the action potential, which is due to a balance of currents created by the influx of calcium, and calcium release from the sarcoplasmic reticulum, and the efflux of potassium ions. The end of the T wave marks the completion of repolarisation of all the ventricular myocytes.

1.1.2 Surface recording of Cardiac Electrical Activity

Willem Einthoven (1860-1927) invented the string galvanometer, the forerunner of the electrocardiographic recorders in use today. Although primitive by modern standards, it laid the foundations for what has become a vast field. He originally proposed the labelling P,Q,R,S,T for the various reflections on the surface electrocardiogram (ECG), although the precise reasons for this are unclear. According to Henson (Henson 1971), Einthoven was influenced by the mathematician Descartes, who employed letters to substitute numbers in calculations and diagrams. Others suggested that he chose these letters as they were fairly central in the alphabet and would therefore permit additional letters either side (such as the subsequent labelling of the 'U' wave (Snellen 1995). In recognition of his work, Einthoven received a Nobel Prize in 1924. Between 1903 and his death in 1927 he published 79 papers on electrocardiography, and is regarded as the undisputed Father of clinical electrocardiography.

The QT interval was later shown to correspond with the timing of ventricular systole by comparing the onset of the first and second heart sounds with the timing of deflections on ECG (Lewis 1912). While the AP reflects the duration of the electrical cycle of a single cell, the QT interval mainly reflects electrical activity of an area of the heart where thousands of cells are repolarising and depolarising slightly out of synchrony. As the electrical wavefront passes through the Purkinje system and through the ventricular muscle, groups of cells depolarise, similar to a line of dominoes falling one after another. This occurs rapidly, and is assisted in normal

hearts by intercellular gap junctions that allow ion exchange and facilitate depolarisation of adjacent cells. The duration of ventricular depolarisation is indicated by the QRS duration. The T wave represents net repolarisation, and T wave duration is a reflection of temporal dispersion of the end of repolarisation within the myocardium. The T wave is of longer duration than the QRS as there is considerable intra-myocardial variation in action potential duration, with endocardial cells tending to have a shorter AP duration (APD) than epicardial cells. In addition, in many animal models, so-called mid myocardial M-cells have been discovered which have a significantly longer APD.

Franz et. al have demonstrated small but significant trans-mural differences in human hearts (Franz et al. 1987). Moore (Moore 1993) published a review on the generation of T waves and temporal heterogeneity in 1993.

Prolongation of the action potential, whether it be due to changes in the electrolytic milieu, pharmacological action or cardiac disease can lead to triggered activity in myocytes due to spontaneous early- (occurring in phase 2 or 3 of the AP) or delayed- (occurring in phase 4) after depolarisations. This, in association with spatial dispersion of refractoriness or anatomical barriers to electrical propagation (such as the scar of an old myocardial infarction) can provide a substrate for sustained ventricular arrhythmias that can ultimately lead to death.

The QT interval is the most easily measured marker of ventricular repolarisation. QT prolongation has been linked to the initiation of arrhythmias in both congenital and acquired conditions. Measurement of QT, and the establishment of 'normal ranges' is essential if we are to be able to compare and contrast patients and populations.

1.2 Factors influencing the QT Interval

Multiple factors have been shown to influence QT interval duration. The most obvious and well known of these is heart rate. This will be discussed in detail below, and in later chapters.

Electrolyte Abnormalities:

Electrolyte abnormalities such as alterations in the concentration of serum potassium (K^+), magnesium (Mg^{2+}), Calcium (Ca^{2+}) can all influence QT by affecting the trans-membrane currents responsible for the cellular action potential, the electrophysiological equivalent of the QT interval. In clinical practice, hypokalaemia is the most commonly observed abnormality responsible for QT prolongation, and in severe cases, or in conjunction with many cardiac and non-cardiac drugs, arrhythmias can occur.

Pharmacological Agents:

Many drugs, both cardiac and non-cardiac have been associated with QT prolongation and have been implicated in the initiation of malignant arrhythmias,

particularly *Torsades des Pointes* (TdP), an unusual polymorphic ventricular tachycardia virtually pathognomonic of QT prolongation. Unfortunately, many drugs cause QT prolongation and TdP as a collateral effect when their primary use is non-cardiac. Macrolide antibiotics such as erythromycin, or antihistamines such as terfenadine are well known examples. More recently, the gut motility drug cisapride was withdrawn due to concerns over the incidence of pro-arrhythmia. Today, almost all new pharmaceutical agents must be screened to some extent for clinical evidence of QT prolongation. There is some evidence to suggest that the risk of arrhythmias is related to the rate corrected QT (QTc) prolongation (Moss 1993) although there is considerable debate as to how best to measure QT, and correct for heart rate. Reasons for this debate will become apparent in later sections.

Pathological States:

As awareness of the significance of QT prolongation increased, over the years we have found evidence of QT prolongation in many conditions including hypothyroidism, anorexia nervosa, depression, heart failure, hypertrophic cardiomyopathy and others. As a consequence, interest has continued to grow in the field.

Given that the QT interval and its prolongation are important in arrhythmogenesis, it has become customary to measure the QT interval. As the most important influencing factor is heart rate, it is necessary to correct for this if we are to be able to comment

on differences between subjects, and different physiological and pathological states. Investigators have been searching for the best way to do this since 1920. Below is a summary of some of the important milestones in methods for the rate correction of the QT interval.

1.3 Correcting QT for changes in Heart Rate:

Early studies in animals made the observation that mechanical systole was shorter at higher heart rates. Waller (Waller 1891) measured the duration of mechanical systole at various heart rates and from the data derived a formula:

$$systole = K\sqrt{cycle}$$

where 'cycle' refers to the inter-beat interval. K was calculated as 0.343 .

In 1920, Bazett published his much quoted paper 'An Analysis Of The Time Relations Of Electrocardiograms' (Bazett 1920). In this work, with Waller's formula as a starting point, he set out to establish whether the same general formula could be applied to the duration of electrical systole in men, women, children and even some infants. Using a number of ECG traces acquired by him, some supplied by a colleague and tracings found in the literature of the time, he calculated K in men and women. He also acquired some data from subjects before and after exercise giving a wide range of heart rates (60 to 180+ beats per minute). From the pooled data he calculated the value of K for men to be 0.368s for electrical systole. In women the

average value of K was longer at 0.399s. He concluded that the duration of the ventricular complex on ECG is a function of the pulse rate and could be readily determined by using Waller's square root formula, and his own value of K. This formula was subsequently relabelled and became $QTc = QT / \sqrt{RR}$, with the corrected QT (QT at an RR interval of one second) replacing K. Bazett was under no illusion that these figures were universally applicable as he states himself that the study was small and the population groups heterogeneous (age ranged from 1 day old infants to octogenarians. In addition, the 'exercise' data was not acquired during exercise but was recorded , on average, several minutes, after the end of exercise. The importance of this point will become apparent in subsequent chapters.

Fridericia published a similar paper in German a few months prior to Bazett (Fridericia 1920). He examined the relationship between QT and heart rate, but differed from Bazett in that he set out by taking QT measurements from ECGs and then calculated the formula which best fitted the QT/RR curves. From his data, he calculated the relationship between QT and the RR interval as $QTc = QT/ \sqrt[3]{RR}$. Unfortunately, perhaps because the article was published in German in a less prominent journal, Fridericia's formula was foreshadowed by Bazett's.

Because of the perceived importance of absolute prolongation of QT and its rate dependence, work has carried on over the ensuing decades in search of the 'perfect' rate correction formula. These are too numerous to mention in detail and instead I will concentrate only on those which have endured the passage of time.

In 1983 Morrison Hodges proposed a linear rate correction formula for QT in steady state conditions in abstract form (Hodges, Salerno and Erlien 1983). From a large database of 607 healthy volunteers (50% male) they calculated a linear best fit correction formula :

$$QTc = QT + 1.75 \times (\text{heart rate} - 60)$$

which they showed provided a better fit of data than the exponential model of Bazett. In addition, when the corrected QT is plotted against heart rate there is no correlation ($r=0.0$) compared to QTc ($r=0.38$, $p<0.001$). It should be pointed out however that this 'linear' formula is linear only when heart rate is used. It is now more conventional to measure QT against the RR interval, and when this formula is converted to use RR, it becomes non-linear.

In 1984, Sarma et al (Sarma et al. 1984) studied 10 volunteers exercising on a bicycle ergometer and six subjects with rate programmable VVI pacemakers. From their previous work in which they found that the relationship between heart rate and repolarisation in conscious dogs was best presented as an empirical exponential formula with variable exponent:

$$QT = A1 - B1 * \text{Exp}(-k1*RR)$$

They assessed the surface QT and its relationship with heart rate in these groups in the same fashion. They found that the fit of QT and RR interval data was far better when the exponential formulae were applied rather than Bazett's formula. Of particular interest, they found that the residuals were far greater for Bazett's formula

when the paced group were studied, showing a great dependence on heart rate. They suggest that the estimation of the variables in their empirical exponential formula would lead to improved correction for heart rate and would be better placed to assess, for example, drug induced changes in repolarisation at varying heart rates than would a fixed formula such as Bazett's.

This was followed in 1992 by another correction formula derived from analysis of a large data-set from the Framingham heart study. The Framingham correction formula (Sagie and Larson and Goldberg 1992), as it came to be known, was derived from analysis of resting ECGs from 5,018 subjects (2,239 mean) with mean age 44 years. The derived formula was:

$$QT_{LC} \text{ (linearly corrected)} = QT + 0.154.(1\text{-}RR)$$

This formula applied equally well to both men and women. Plotting QT_{LC} against the range of RR intervals, the corrected QT is constant. This was in contrast to QTc, where a significant correlation remained between the rate corrected QT and RR, implying that it could not be correcting adequately for rate.

1.4 Comparative Studies of QT Correction Formulae

In 1996, the controversy over which correction formula to use prompted James Molnar et al (Molnar et al. 1996) to perform a comparative study. They analysed ambulatory ECG data to examine the accuracy of 5 formulae: simple Bazett's,

modified Bazett's, linear (Framingham), modified Fridericia's, and exponential (Sarma's) (Sarma et al. 1984). Their methodology was to divide Holter data into 5 minute segments and calculate the mean RR and QT with a computer assisted method for QT measurement. They then calculated the corrected QT at an RR interval of one second (QT60) and generated best fit lines for each of the 5 correction formulae.

The relative goodness of fit of the data when 'corrected' by each of the 5 formulae was assessed from mean square residuals (MSRs):

$$MSR = RSS/(N-P)$$

where RSS is the residual sum of squares, N is the number of observations and P the number of regression parameters in the formula. They then went on to compare separately the pooled data from all 21 subjects with generated ideal curves from the correction formulae, and curves generated for each individual with the correction formulae. They ranked the formulae by the MSRs and found that the grouped population data was best corrected by Fridericia's formula but there was little overall difference between each of the formulae. When curves constructed for each individual were compared with individual curves generated by the correction formulae, Sarma's exponential formula was best. They also plotted calculated corrected QT intervals through a range of heart rates for all formulae, again with the hypothesis that an ideal correction formula would give a regression line with gradient zero. They found that for individual data, all but Bazett's formula achieved this. For the group data, all the formulae failed in this respect, with deviations in QTc of as much as 80 ms over a 1s range of RR interval.

They concluded from this study that none of the formulae is ideal. They also raised the important point that although heart rate is the most important determinant of QT interval, other variables such as autonomic tone, drugs, electrolyte abnormalities and disease states also have an important role. Nonetheless, they stated that all formulae using individually calculated regression parameters provided excellent and equivalent QT correction. When group based data was used, acceptable correction for rate was not obtained. They also proposed that when small changes in QT are important, Holter data should be used to provide a sufficiently wide range of heart rates.

In September 1999, Marek Malik's group (Aytemir et al. 1999) published an article regarding the abilities of the various rate correction formulae in exercise ECGs. They studied 21 healthy volunteers who were subjected to a bicycle exercise protocol with 15W effort increments every 2 minutes until a target heart rate of 120 beats per minute was achieved. 12-lead digital ECGs were taken every 30 seconds. Using a Marquette package for QT analysis, the average QT waveform from the 12 leads was processed automatically. Heart rate measurements were converted to RR intervals and for each pair of QT and RR values, a QTc was calculated with each of 5 formulae (Bazett's, Fridericia, Hodges, Framingham and nomogram (QTc = QT + correction factor). Again, QTc/RR regression slopes were calculated.

The Framingham formula led to a positive relationship between QTc and RR (0.0228+/- 0.0451) whereas all the others produced a negative relationship of similar

amplitude. The null hypothesis, i.e. that QTc values are independent of the RR interval was accepted only for Fridericias formula (p=0.44). Comparing rest with peak exercise, they demonstrated, as expected from the QTc/RR regression slopes, that with the Framingham formula, QTc decreases with exercise while the others show an apparent increase. Again, differences in QTc with exercise are not significant when Fridericia's cube root formula is used.

The span of QTc values was narrow at rest and the difference betweeen formulae was small (14ms) whereas at peak exercise, there was a much larger difference (376ms for Fridericia to 419ms for Bazett's). Their conclusions are similar to those of Molnar et al., namely, that it is dangerous to apply one *ad hoc* correction formula in any study as important over- or under-correction may arise. They raised the point that during exercise, not only does heart rate increase, but sympathetic drive increases, acidosis occurs and body temperature rises. All of these factors are likely to alter the relationship between heart rate and repolarisation.

Later that year, Malik's group published another paper examining several generic formulae each with three degrees of freedom (Hnatkova and Malik 1999). These included hyperparabolic, hyperhyperbolic, algorithmic, negative exponential, inverse tangent, hyperbolic tangent and inverse hyperbolic sign functions. Resting ECGs from 1100 healthy subjects were studied, and for each correction formula, the different combinations of variables was found that provided the best fit. Linear regression analysis was used to estimate values for the adjustable parameters of each

formula. Gradual adjustment of one parameter allowed estimation of the other two parameters to give the best fit of data.

The appropriateness and success of each QT prediction was assessed by calculating the sum of squared residuals ($RS= QT- QT_{estimated}$). They found in this comprehensive study of correction formula that almost identical best-fit lines can be achieved regardless of the specific form of the regression model. They also suggested that "further search for a more complicated and more advanced correction formula is likely to be fruitless". They concluded that different datasets of QT/RR would lead to different optimum regression fits and suggest that it would be better to construct an optimum regression model for each particular dataset.

1.5 Influence of the Autonomic Nervous System on QT Duration

The heart receives rich autonomic innervation from both the sympathetic and parasympathetic nervous system which contain both efferent and afferent fibres. Pre-ganglionic sympathetic fibres emerge from the spine and synapse in the cervical and upper thoracic ganglia (the stellate ganglia). From these emerge the cardiac sympathetic nerves, the endings of which can be found in both atria and ventricles alike. The parasympathetic nerves arise in the vagal nucleus in the medulla and synapse in intra-cardiac ganglia.

Stimulation of the sympathetic nerves results in a more rapid rate of diastolic depolarisation in the sino-atrial node, increasing the heart rate. In addition, conduction in the atrioventricular node is also accelerated with reduction in the refractory period. This maintains an appropriate A-V delay for optimum cardiac filling and enables conduction of more frequent impulses, preventing AV block at higher atrial rates. At ventricular level, the force of contraction is increased by catecholamines and the action potential duration (APD) shortens. The influence of the sympathetic nervous system on the ventricles is modulated to some extent by cholinergic activity and is therefore dependent to some extent on vagal innervation.

Vagal stimulation prolongs action potential duration by antagonising sympathetic activity at muscarinic receptors, and ventricular refractory period is shortened by atropine. At rest, vagal tone exerts a significant effect on ventricular repolarisation and this effect is seen in the presence of beta-blockade. This may be the mechanism whereby increased parasympathetic activity has been shown to protect against ventricular fibrillation (Schwartz and Stone and Brown 1976).

In 1983, Fananapazir et. al (Fananapazir and Bennett and Faragher 1983) conducted an elegant study which highlighted the contribution the autonomic nervous system makes to QT shortening on exercise. Their hypothesis was that the catecholamines from increased activity of the sympathetic nervous system were responsible for a significant proportion of the shortening seen in the QT interval. They studied 24 patients with dual chamber (DDD) pacemakers. They measured QT shortening during

Bruce protocol exercise testing during both fixed rate ventricular pacing (VVI) and atrial synchronised ventricular pacing DDD). They then repeated the exercise tests after acute administration of beta blockade with 100mg of oral atenolol. They also used incremental atrial and ventricular pacing at rest to assess purely rate related QT shortening. They demonstrated that only about 50% of the QT shortening seen during exercise is due to rate change. They also demonstrated that the QT shortening seen in the fixed rate ventricular pacing group on exercise was abolished by beta blockade. Compelling evidence that catecholamines exert an independent action on QT interval and that this, in terms of magnitude, is at least as important as heart rate.

In 1986, Bexton, Vallin and Camm published further evidence of the impact of the autonomic nervous system on circadian variation of the QT interval (Bexton and Vallin and Camm 1986). They studied three distinct groups for comparison. The first group consisted of 6 patients with fixed rate ventricular pacemakers. The second group was composed of 6 patients who had received heart transplants (and the heart was therefore denervate). The third group was made up of nine insulin dependent diabetics with autonomic neuropathy. All subjects underwent 24h ambulatory ECG recordings. Hourly QT and RR intervals were measured for each subject by taking mean values from 10 consecutive beats. QT intervals were corrected for heart rate using Bazett's formula. Variation in QTc duration was expressed as percentage deviation from the 24h mean QT for each individual.

In the pacemaker group there was considerable circadian variation in QTc, with significantly longer values during sleep. In the transplant group there was little

variation in heart rate during the 24h period. Circadian variation in QTc was present however, although blunted. QTc was longer during the night when circulating catecholamines were at their lowest level.

In the diabetic group who all had proven autonomic neuropathy, there was no circadian variation in QT interval. These patients are said not to respond to neurally mediated changes in autonomic tone. These patients would also be expected to have reduced circulating catecholamine levels as has been shown in previous studies (Barnes, Fitzgerald and Dollery 1982). They concluded from this that the normal circadian variation in QT and QTc duration is influenced by the autonomic nervous system and by circulating catecholamines.

It is thought, from research involving patients with the long QT syndrome, that sympathovagal balance plays a critical role in the triggering of arrhythmias. Certain subsets of patients, particularly those with LQT1 which corresponds with a mutation in the gene KVLQT1 (which codes for a potassium channel), are more likely to experience arrhythmias associated with acute arousal (Ali et al. 2000). These events are more likely to be triggered when sympathetic activity is high and increasing, and vagal tone is withdrawn. Indeed, one of the accepted therapies for patients with this disorder was ablation or transection of the left cervical stellate ganglion (Schwartz et al. 1991). Indeed, prior to the identification of mutations of genes encoding for ion channels, the aetiology of the long QT syndromes was thought to be due to an

asymmetry in the balance between the right and left sided sympathetic innervation of the heart (Schwartz, Periti and Malliani 1975).

1.6 Influence of Anti-arrhythmic medication on the QT Interval

Anti-arrhythmic medications exert their effects by modifying one or more of the ion currents and therefore affecting excitability, automaticity, or the action potential duration. The Vaughan-Williams classification initially divided anti-arrhythmic drugs into four groups based upon their mode of action. This was later expanded into the Singh-Hauswirth-Harrison-Vaughan Williams (S-H-H-VW) Classification with subdivision of class 1 into three subgroups. This classification is laid out in the table 1.1. While the modification of the action potential is designed to slow the propagation of impulses and reduce the possibility of a re-entrant circuit sustaining arrhythmias, they can, in some individuals, promote triggered activity. This is particularly true of the class 1C and class 3 agents. Major studies assessing the ability of these drugs to improve survival following myocardial infarction in individuals without a history of malignant arrhythmias (e.g. CAST (1989) - class Ic), SWORD- class III (Waldo, Camm and de Ruyter 1996) produced an excess of deaths in the treatment arms. The excess of deaths is a reflection of the ability of these agents to promote arrhythmia through triggered activity. If the risk of proarrhythmia exceeds the patients intrinsic risk of malignant arrhythmias, then no benefit, or an adverse outcome may be seen. These studies enrolled patients who had not had malignant arrhythmias, but had

ventricular ectopy on Holter monitoring. With the benefit of hindsight, we are able to say that their relatively low risk of arrhythmias was outweighed by the slightly higher risk of drug induced pro-arrhythmia.

Class of Drug	Examples	Primary site of Action	Mechanism(s)	Uses
1a	Quinidine Procainamide Disopyramide	HP, A, V	Slow dV/dt phase 0; prolongation of repolarisation and PR and QRS duration	SVT, VT
1b	Lignocaine Mexilitine Phenytoin	V	Limited effect on phase 0 dV/dt. Shortens repolarisation and hence QT	VT, VF
1c	Flecainide Propafenone	HP, V	Slows dV/dt. Little effect on repolarisation. Marked prolongation of PR and QRS	SVT, VT
2	βblockers e.g. esmolol atenolol	SAN, AVN	Slows rate of rise of phase 4 therefore reduced automaticity of SAN and AVN. Suppresses catecholamine induced surge in pacemaker current, Ca current and Na current and delayed rectifier (I_{Ks})	Tachyarrhythmias
3	Amiodarone Sotalol	A, V, AVN, SAN, HP, AccP	Increased APD by blocking I_{Kr}, hence prolonged QT. SAN and AVN slightly suppressed.	AF, Aflutter, SVT, AVNRT, AVRT, VT, VF
4	Calcium channel antagonists e.g. verapamil	AVN	Depress phase 2 and 3 of the action potential by blocking the slow Ca current.	Atrial arrhythmias, AVNRT

Table 1.1 : The Singh-Hauswirth-Harrison-Vaughan Williams (S-H-H-VW) Classification. A, Atrium. V, ventricle. AVN, atrioventricular node. SAN, sino-atrial node. HP, His-Purkinje system, AccP, accessory pathway. Aflutter, atrial flutter. SVT, supraventricular tachycardia. VT, ventricular tachycardia. AVNRT, AV node reciprocating tachycardia. AVRT, atrioventricular reciprocating tachycardia. VF, ventricular fibrillation.

These two studies have highlighted two important points: firstly, that our existing non-invasive methods of risk stratification of patients with heart disease are lacking specificity. Secondly, as a consequence of the first, powerful anti-arrhythmic agents which exert effects on the action potential can result in death. Unfortunately, as a consequence of these studies, sotalol and class Ic agents have fallen out of favour for the treatment of patients with ischaemic heart disease.

Further discussion of the effects of class 3 agents is merited as it highlights one of the problems associated with estimation of rate independent QT change. Class 3 agents such as sotalol and dofetilide cause QT prolongation by interfering with the normal function of the inward potassium rectifier current (I_{Kr}). However, they exert more effect on the action potential at low heart rates than at high heart rates ('reverse use dependence'). This was proposed to be due to the binding of these agents to closed or inactive channels in diastole. More recently, this theory has come under scrutiny as it is found that with cloned channels this does not appear to be true. Other agents such as almokalant have been shown to block IKr in a use-dependent fashion yet show reverse-use-dependent prolongation of the action potential. This means that at low heart rates, regardless of the exact mechanism at a cellular or channel level, the consequence of this phenomenon is greater prolongation of action potential and QT interval during bradycardias or following a post extrasystolic beat. This is obviously not the ideal situation, as an anti-arrhythmic drug which had maintained or enhanced anti-arrhythmic efficacy during tachycardias would be an advantage, particularly for terminating arrhythmias.

The rate dependent effects of antiarrhythmic agents are important in the context of rate correction formulae. If we were to use Bazett's formula to calculate the corrected QT interval for a patient taking sotalol, this would enforce a constant relationship between QT and RR at all heart rates. During bradycardias, the QT would be more prolonged by the sotalol, leading to an even greater value of QTc. If however we correct QT for heart rate during a tachycardia, the sotalol will be having far less effect of repolarisation and QT, and the QTc may be normal. Therefore, when this approach to QT correction also makes the assumption that the QT/RR curve bears a square-root relationship to heart rate under both circumstances. Rate correction formulae must therefore be applied with caution when these agents are in use, with particular attention being paid to heart rates on serial recordings.

1.7 Conclusions

The QT interval is always affected by heart rate but the relationship differs according to the populations studied. The method of acquiring QT and RR data and the physiological circumstances of the data recording (e.g. resting ECG, ambulatory Holter or exercise ECG) will also affect the estimated relationship. Everyone agrees that the QT interval is important, but no one can agree how best to correct for heart rate. All correction formulae have been shown to be better than others in certain populations, but, as Malik suggests, one should perhaps find which one works best for the given population before making comparisons.

Given that sympathetic tone has been shown to influence QT interval, even when changes in heart rate are absent (as in paced individuals), and that in normal subjects, exercise produces an increase in sympathetic drive and an increase in heart rate, is it realistic to expect the relationship between QT and heart rate to be the same at rest as during exercise? The fact that it has been shown that the slope of QT/RR curves or lines varies throughout the day, as does QTc (to varying degrees, depending on the correction formula used), and to differing extents depending on pathologies, this would suggest that the mode of describing QT dynamics should be more detailed. As we enter an era when technology allows us to automatically analyse large quantities of data from, for example, Holter recordings, new approaches are needed to assess the relationship between QT and heart rate or the RR interval. Holter recordings give us the opportunity to see 'a day in the life' of ventricular repolarisation from patients. The opportunity also arises in some cases to assess changes in the relationship with time, perhaps leading up to arrhythmias. Indeed, the way the relationship between QT and RR changes in response to internal and external factors may be more important than QTc alone. We should perhaps be thinking not just in terms of QTc, but also attempt to describe the curve or line on which QTc sits. This line or curve may be allowed to vary throughout the day and should perhaps be determined for each individual separately, and mean values of QTc and the variable used to describe the curve for population groups could be compared for each study.

The ultimate goal of research into QT should be to describe cardiac repolarisation as it exists in individuals most of the time, when heart rate is changing over a wide

physiological range. The forced application of a 'universal' rate correction formula to distinct populations is questionable when differences have already been shown to exist between men and women, patients and volunteers, those on anti-arrhythmics and those not, both in terms of 'QTc' and the slope of QT/RR plots. When so many correction formulae exist, all with merits and demerits, why do we continue to pursue the 'Holy Grail' of a universal method for the heart rate correction of QT?

Chapter 2

Adaptation of the QT Interval to Sudden and Gradual Rate Changes: Implications for the analysis of non-steady state ECG recordings.

2.1 Introduction

The adaptation of the QT interval to changes in heart rate is not instantaneous. This complicates estimation of the QT/RR relationship, particularly when the underlying relationship is likely to be influenced by the concomitant variation in autonomic tone that often occurs when heart rate changes. Many investigators have studied the characteristics of the adaptation of QT to changes in RR. It has been widely shown that there are two phases of adaptation: 1) A fast component which depends on the preceding RR interval and causes an immediate small change in QT, and 2) A slow component which contributes to long term adaptation. I will discuss below some of the work which has furthered our understanding of this phenomenon.

2.2 Characteristics of the Adaptation of QT to Heart Rate Changes

In 1998 Michael Franz and colleagues published a paper on measured intracardiac monophasic action potentials (MAPs) in human hearts in-vivo (Franz et al 1998). They showed that after a single premature stimulus, the APD of the subsequent beat was related to the extra-stimulus cycle length. By plotting the post-extra-stimulus APD against the extrastimulus cycle length (CL) one can construct the 'electrical restitution curve' for the myocardium. The earlier the extrastimulus becomes, the greater the change in APD. After a sudden sustained step in cycle length, the APD underwent the initial small sudden change in APD followed by a delayed adaptation before reaching a new steady state only after several minutes. They found that the initial small jump in APD equated to an average of approximately 25% of the

adaptation required to reach steady state (range 8.9-45%). The delayed component of adaptation which corresponds to (100-rapid component) % required an average of 2.6 minutes to reach steady state (range 1.8 – 3.2). They concluded that the overall relationship between the steady state APD and CL was linear (r=0.995) although they excluded all the data at CL>900ms at which point all the plots clearly plateaued. If these data were included, their plots clearly show a curvilinear relationship. They concluded that the divergence between steady state and non-steady state APDs was an important factor to be considered in rate correction formulae.

Shortly after the publication of this paper, Lau et al demonstrated the same phenomenon in changes in the surface QT interval in ventricular paced subjects with new onset complete heart block(Lau et al. 1988). They chose this model to avoid interference from changes in the autonomic nervous system. They found that the mean time for the QT interval to reach 90% of steady state was 136+/16 seconds (SEM) when the heart rate was increasing and 189+/-25 when the heart rate was decreasing. They found the time course of QT adaptation to be exponential and characterised by time constants of 49s and 60s when the heart rate was increasing and decreasing respectively. They concluded that the adaptation is biphasic with rapid change in the first minute accounting for 50% of the adaptation and a slower phase lasting for several minutes. The sudden instantaneous change relating to the first CL at the new heart rate was not identified due to their methodology, however it would seem that the first QT sampling point was at 15 seconds. One of the important points in the discussion is that they highlight the influence measurement of QT prior to attainment of steady state would have on the modified Bazett corrected QT. Namely that for increasing heart rates (decreasing RR), if measured early in adaptation QTc would be overestimated and conversely, underestimated for decreasing heart rates.

A study undertaken by Jonnalagedda et al (Jonnalagedda et al. 1987) studied QT hysteresis in men during exercise. They exercised 14 subjects, ranging in age from 16 to 71 on a treadmill following the Bruce protocol. ECGs were measured continuously on magnetic tape and QT and RR intervals were measured semi-automatically. They fitted the QT and RR data to an exponential formula ($QT = A - B \times Exp(-k.RR)$) where A, B and k are the regression parameters. They then compared the best-fit curves for exercise and recovery and found that the recovery QT values were shorter than on exercise for similar RR intervals. In some individuals the late recovery QT intervals were longer than the early exercise values, i.e the QT/RR lines crossed over. The recovery hysteresis curves were S shaped in many individuals. Considerable variation was seen in the relationship between exercise and recovery curves between individuals and they attributed this to the wide variation in age, cardiac disease and medications in their heterogeneous group.

If one reviews this study in the context of the data from Franz, it would appear to fit quite well. The QT changes on exercise would be affected by adaptation lag and therefore during exercise QT would lag behind RR change and be longer than a steady state QT at that heart rate. Equally, in recovery, QT may still be shortening in initial recovery, and subsequent lengthening in QT will lag behind RR lengthening, explaining the curves. Knowing that the sympathetic nervous system will increase in activity, with withdrawal of parasympathetic tone on exercise, the two combining to affect QT shortening. It has been shown that plasma adrenaline and noradrenaline levels increase for up to 3 minutes into recovery despite a decrease in heart rate (Hagberg et al. 1979, Dimsdale et al. 1984) followed by a sharp decline. This may be partly responsible for the initial further shortening of QT in recovery seen in some subjects.

Through the years, other investigators have demonstrated a similar biphasic relationship between RR change and QT in various species and and have also assessed the impact of QT prolonging drugs on QT adaptation. Lee et al (Lee et al. 1999) studied the adaptation of QT to changes in RR as measured through a permanent pacemaker lead for sudden steps in RR. They validated this method against the epicardial APD measured with the intracardiac catheters described by Franz. They demonstrated that the stimulus to T_{end} time correlated well with APD. They also described the QT adaptation as being biphasic, with the early adaptation having a very short time constant, with a $t_{1/2}$ of 1 beat. The slower adaptation phase had a $t_{1/2}$ of 1,386 beats at an RR interval of 400ms (9.24 minutes).

Padrini et al studied QT shortening in an isolated guinea pig heart model under the effects of d-sotalol and amiodarone (Padrini et al. 1997). As class III drugs can be associated with pro-arrhythmia, often in the context of a sudden pause in heart rate or during bradycardias, they assessed the two phases of QT rate adaptation. They found that at high heart rates, d-sotalol and amiodarone did not cause significant QT lengthening and that they may enhance adaptation to rate, reducing the possibility of 'R on T' phenomena inducing malignant arrhythmias. This, they concluded, was mainly due to an enhancement of the rapid early phase of adaptation.

Clearly, QT rate adaptation is an essential consideration in the estimation of the QT/RR relationship from data where heart rate varies, and hence QTc. It raises a question mark over the validity of the calculation and application of QT/RR correction formulae derived in exercise studies if the peak heart rate for any stage of the protocol was not maintained for several minutes before measurements were made.

2.3 Estimation of the QT/RR Relationship From Ambulatory Recordings

Technology has progressed at an incredible rate over the past decade. With increased computer processing power it has become possible to create sophisticated automated algorithms for detection of the end of the T wave. This has allowed the analysis of long-term ECG recordings. From this, interest has grown in the assessment of dynamic changes in QT measured from Holter recordings. Taking into consideration the work covered in previous pages, a new approach to the analysis of QT may be needed.

Early attempts to estimate the QT/RR relationship from long term recordings have divided the recording into lengthy periods and constructing QT/RR plots for these sections to allow comparison between time periods. These long segments of recording have the advantage of providing data over a wide range of heart rates, and also of reducing the impact of errors introduce by noisy or ectopic beats. In addition, the QT adaptation lag will tend to be averaged out to some extent as the value derived for the QT/RR relationship will be a best-fit line of the hysteresis loops. All beats are included in these QT/RR plots and best-fit lines are estimated usually using a linear regression model. Using this approach it is possible to demonstrate that the QT interval is longer at night compared to identical heart rates during the day, a reflection of the differences in autonomic tone.

In 1992, Merri et al (Merri et al. 1992) used such a method to compare normal subjects (NS) with patients with the long QT syndrome (LQTS). They measured the interval from the peak of the R wave to the peak of the T wave (RTm). Their reasons

for doing this were that the onset of the Q wave is variable relative to the peak of the R wave, and T_{end} detection is technically difficult to determine in many subjects and is subject to interference from noisy recordings. In addition, they have shown in previous work that the rate dependent change in QT is mainly concentrated in the initial portion of the T wave to the apex. They demonstrated that the mean 24h slope of the RTm/RR chart was greater in LQTS than in NS. In addition, as some of the LQTS patients were β-blocked, they repeated recordings in 6 NS after β-blockade. This further reduced the mean RTm/RR slopes in the normal subjects, implying that an even greater difference may exist in slope between LQTS and NS.

A more sophisticated method was proposed in 1998 by Badilini, Maison-Blanche, Childers and Coumel (Badilini et al. 1998). They recognised the significance of QT adaptation lag on QT dynamics and developed a sophisticated automated method to minimise its impact on measurements of the QT/RR relationship. Their 'Selective Beat Averaging' (SBA) approach is a means of analysing recordings taking paired QT and RR intervals but only using QT intervals where heart rate has been stable within a predefined narrow range for the preceding minute. This thereby attempts to exclude most non-steady state data. They found using this method that the steady-state QT/RR slope was modelled well by a linear formula QTo = 0.161RR+0.254 (r= 0.97), whereas analysing non-steady-state periods, the slope was much lower and described by QTo = 0.094RR + 304; r = 0.94, where QTo is the interval from the start of the Q wave to the end of the T wave (T_{offset}). Again, by dividing the QT/RR relationship into day and night segments, they demonstrated lower slopes during sleep. Unfortunately, as they state themselves, the main limitation of the method is that SBA provides a long-term analysis of repolarisation at steady-state and by

definition, 'all transient phenomena have been ruled out and cannot be taken into account when using this approach'.

Another method which deserves mention has taken an entirely different approach to the description of QT/RR dynamics. 'Beat-to-beat QT Interval Variability' was described by Berger et al in 1997 (Berger et al. 1997). Their hypothesis was that in many cardiac conditions, the heart rate variability (HRV) is reduced. This has been shown to correspond with a relative reduction in parasympathetic tone and an increase in sympathetic tone. Despite this, the QT interval shows considerable variation. Their method uses an automated technique for measurement of QT and RR from Holter recordings. By comparing a subjects variation in RR with the variation in QT over a period of time, it may be possible to show that, relative to changes in RR intervals, there is a greater change in QT, potentially indicating a discordance between the two that may predispose to arrhythmias. One of the methodological differences is that a reference QT interval is selected by the operator to act as a template and is defined beat *k*. Each beat of a 256 second epoch is then compared with *k* . From this, the QT variance (QTv) and mean QT (QTm) are calculated and compared with heart rate variance (HRV) and mean heart rate (HRm). QT variability index is calculated for each epoch as being:

$$QTVI = \log_{10} [(QTv/QTm^2) / (HRv/HRm^2)]$$

Coherence between changes in heart rate and QT is calculated by comparing the frequency and magnitude of QT change relative to the frequency and magnitude of RR change. In this paper, they compared 60 controls (NS) to 83 patients with cardiac failure (HF). They found, as expected from heart rate variability studies, that HRV was low in HF. In contrast, QTV was elevated relative to controls and varied in an

unpredictable fashion. This resulted in a marked elevation in the QTVI in HF. They found that this correlated with NYHA class but not with ejection fraction, a finding that may point more towards derangements in autonomic tone being responsible for this. The coherence between HR and QT was much lower in HF. They conclude that this method, although not actually describing the relationship between QT and RR but the sensitivity of QT to changes in RR, may be implicated in the arrhythmic risk of patients with HF.

Using the same method, Atiga et al (Atiga et al. 2000) demonstrated a similar finding in patients with hypertrophic cardiomyopathy. In addition, they found that in patients with a particular mutation felt to be responsible for a high risk of arrhythmias, the QTVI and coherence were more abnormal than patients with more 'benign' mutations. This method shows great promise and is based upon the analysis of a short ECG recording (256s). It links the changes in QT to changes in RR. One of the distinct advantages is that the problems of rate dependence of QT and QT adaptation lag do not seem to be confounding factors with this approach. It may also allow examination of pre-event periods from Holter to allow comparison with reference periods to assess changes in QT interval dynamicity. To date, no publications have appeared using this method in that context.

2.4 Conclusions

The analysis of ambulatory data from patients should provide a more balanced picture of their cardiac repolarisation properties. Apart from the technical difficulties of accurate and reliable measurement of the end of the T wave, exclusion of noisy segments and the limited number of leads available, we must also consider the

phenomenon of QT adaptation lag. In order to be able to comment on short and long term changes we must either find an approach that circumvents or tackles this issue. As other investigators have shown, the analysis of non-steady state data provides significantly different results.

Investigators have shown that patients and healthy subjects not only have a longer 'corrected' QT but also steeper QT/RR slopes. These slopes will be influenced by the time of day and medications such as sympatholytic agents not to mention anti-arrhythmic drugs.

If we are to assess repolarisation changes in humans from ambulatory recordings, it would seem that several things are essential. The method must be able to:

1. Reliably measure RR and QT intervals
2. Measurements must be reproducible
3. QT adaptation lag must be taken into account
4. The QT/RR relationship over short and long term segments must be expressible in rate independent variables
5. Individual QT/RR characteristics should be calculated for individual subjects and these variables averaged for the population, rather than grouping QT and RR data.

Chapter 3

Methodology for the Acquisition and Analysis of Beat-to Beat QT Interval Dynamicity from Holter ECG Recordings

3.1 Introduction

In May 1998 at the International Society of Holter and Non-invasive Electrocardiology (ISHNE) congress in Ulm, James Neilson of the Department of Medical Physics, University of Edinburgh proposed a novel method for continuous estimation of the QT/RR relationship (Neilson 2000). This method differed from previous methods in many ways.

Methods for analysis of the QT/RR relationship have attempted to bypass the problem of QT adaptation lag by concentrating on the steady-state periods. Neilson's method attempts to compensate for the adaptation lag by applying a mathematical model to remove it and therefore allow continuous assessment of the underlying QT/RR relationship. As mentioned in the preceding chapters, most methods for estimating the rate corrected QT assumed that the QT/RR relationship was constant, yet investigators had shown that the relationship varies between populations, individuals, and also exhibits considerable circadian variation. The Neilson method has the added advantage that the relationship is continuously calculated and can be described at any time or heart rate by a formula with only two variables

The following pages explain the various stages in acquiring and analysing the dynamic QT-RR data. As this is the method used throughout the thesis, it will be explained in detail now to avoid repetition is required in subsequent chapters.

3.2 Acquisition of Ambulatory ECG Recordings

ECG recordings were acquired using standard analogue 2 channel 'Tracker 2' recorders (Reynolds Medical, Hertford, England). Electrodes were of the type R-00-5 (Blue Sensor) for all recordings. The importance of good skin preparation cannot be understated as recordings of high quality are required for measurement of the T wave. The skin was prepared by shaving any chest hairs that might interfere with electrode contact. The skin is then gently abraded to remove dry skin cells with a gauze swab and granular ECG jelly. The chest electrodes are then placed in standard positions to give bipolar thoracic leads CM1 and CM5 (Figure 3.1).

The quality of the 'hook-up' for each electrode was tested using an in-house impedance testing module. This measures the electrical impedance between the individual electrodes in turn versus an additional reference electrode. If the impedance was considered unacceptably high for any one electrode, it was replaced and/or re-positioned. The morphology of the T waves for each channel was assessed at the time of electrode placement using a portable oscilloscope. If T waves were of low amplitude in one or both channels, the electrodes were re-positioned to rectify this. Repositioning of electrodes was generally not necessary as there was usually a signal of sufficient amplitude with clear T wave morphology in at least one channel.

Recordings were made onto standard audiocassettes (TDK D90) which will record over 24 hours of ECG in two channels. Time track data is also recorded, and the Trackers have internal clocks set to real-time. This time-track data enables

compensation of minor fluctuations in recording or playback speed and synchronisation of the recording with events reported or times of day.

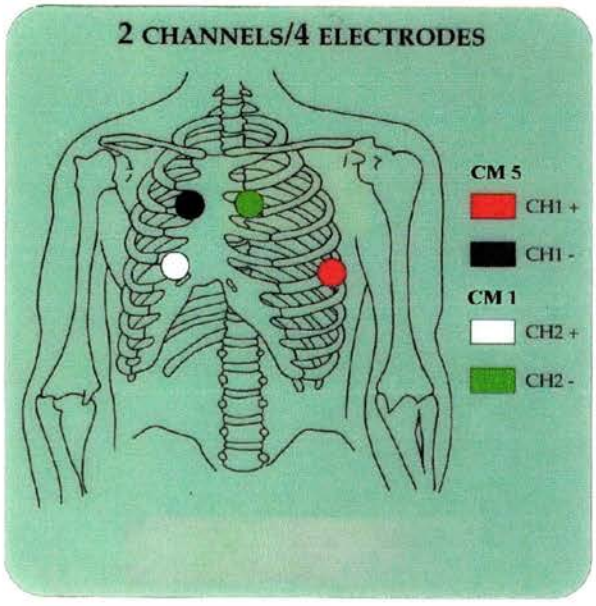


Figure 3.1 Diagrammatic illustration of the position of the 4 electrodes to give two channels, CM1 (green and white) and CM5 (red and black)

3.3 Measurement of QT and RR data

The recordings were analysed at high speed on a 'Pathfinder' Arrhythmia Analyser. The Pathfinder measures each RR interval and the associated QT interval. Beats were automatically excluded if they:

a) were of abnormal shape (e.g. aberrants or distorted by noise)

b) had an RR interval <66% or > 180% of the prevailing beat,

c) were beats with an RR cycle length of > 2.5s.

d) The beat preceding and the beat following aberrants were also excluded.

After the exclusion of these beats, the timing of each RR interval was established. Following this, time windows were set up relative to the QRS wave. The Q onset is determined by first determining the centre of the R wave (zero slope turnover point of the first derivative). Q onset is set by default at a fixed period prior to the centre of the QRS. Minor manual adjustment of Q onset is possible and occasionally required prior to starting and sometimes during playback due to the natural variations in QRS duration.

A T wave 'window' relative to the QRS waves is set up to exclude false readings of T wave parameters from other parts of the ECG due to U waves, P waves and noise. The T wave window adjusts automatically for changes in heart rate. T_{apex} is determined as the zero slope turnover point between the upstroke and downstroke of the T wave (figure 3.2). The end of the T wave (T_{end}) is determined as being the point at which the slope of the T wave falls below a pre-determined fraction of the maximum slope. Although T_{end} is also adjustable, the settings used in default mode have been determined as the average point of T_{end} as determined by the mean values of QT from rhythm strips from the Pathfinder measured by a panel of seven clinicians experienced in measurement of the QT interval.

During playback, on-screen continuous markers of Q_{onset} and T_{end} allow visual validation of measurements by the operator. Noisy segments were automatically edited out, along with premature supra-ventricular and ventricular beats. Continuous checks are made for non-physiological changes in QT or RR and these beats were

auto-rejected and acquisition suspended until stability returned. All QT and RR interval data is stored on a personal computer for offline analysis. The accuracy and correlation of the automatic versus manual measurement of the QT interval has been independently validated and reported elsewhere (Lande et al. 2000).

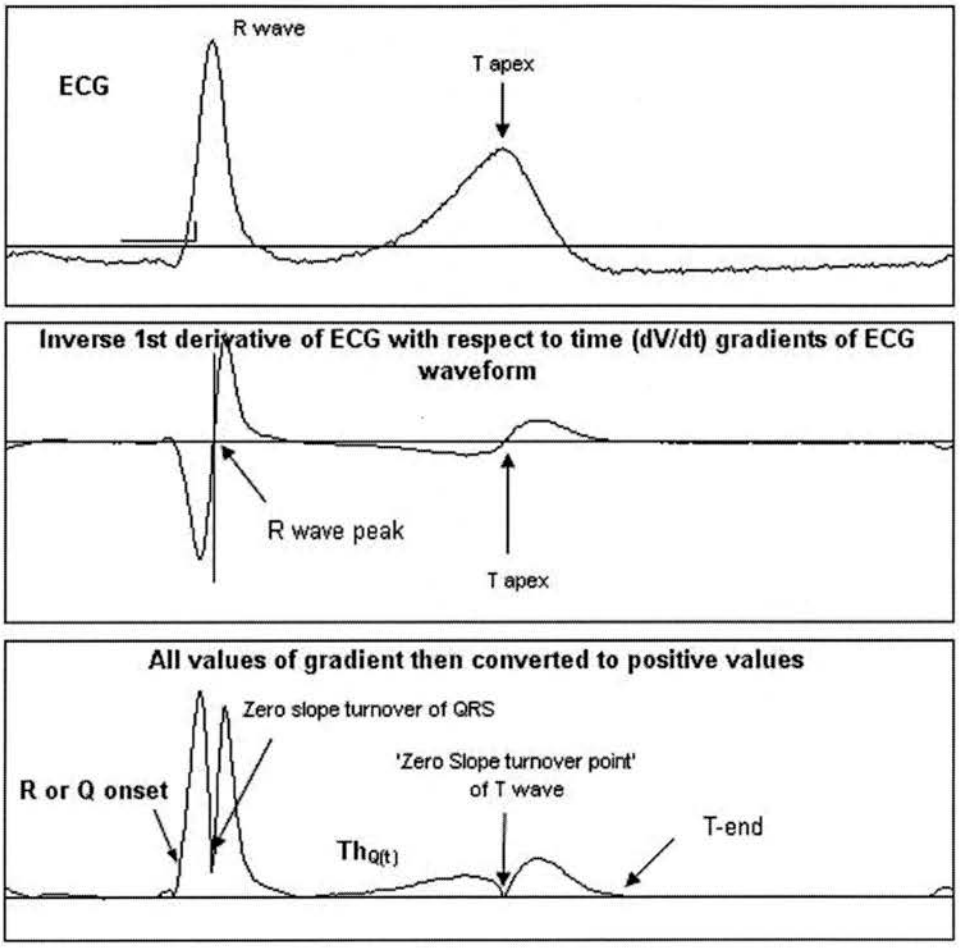


Figure 3.2:

Electronically acquired ECG waveform (upper panel), the inverse first derivative of the wave form (-dV/dt) (middle panel), and the modulated derivative (lower panel) indicating how the analyser recognises T_{apex} (zero-slope turnover point, lower panel), which 'opens' the time-window to start looking for T_{end} (defined as when the gradient of the T downslope drops below a preset threshold.

3.4 Assessment of the QT/RR Relationship with QT Lag Compensation

The estimation of the dynamic QT/RR relationship takes place in stages that are detailed below

3.4.1 Error correction

The QT and RR data are replayed at high speed and compared with a simultaneously acquired (at the time of tape playback) noise signal. When the signal to noise (S/N) ratio crosses a pre-determined threshold, the QT and RR data are edited out. This 'error correction' gives a final result for percentage of data corrected. This value is then taken into consideration when deciding whether acquired data is suitable for further analysis. In addition, beats with sudden non-physiological changes in the QT which are due to errors in measurement of T_{end}, generally due to noise or morphology change in the T wave, are edited out automatically.

This 'error correction' programme gives a value in percent of the data edited out from recordings. As a rule, only recordings where less than 20% has been edited are used for analysis.

3.4.2 Compensation for QT adaptation lag

Theoretical aspects of the method

From watching dynamic QT/RR plots from ambulatory recordings, it is possible to see that the plot displays hysteresis loops due to the lag in adaptation of QT to RR. If

the heart rate remains stable for long enough (several minutes), the QT is able to 'catch up' with the RR interval and will lie on the QT/RR curve described as the 'steady state characteristic' (SSC). As mentioned previously, establishing the QT/RR relationship from data acquired in this way would result in the loss of large amounts of data. In addition, as the QT/RR relationship changes constantly during the day, comparing points at different heart rates at different times of day may be comparing points on different steady state curves.

From this it becomes clear that if the QT adaptation lag can be compensated for, the changes in QT and RR would be synchronised in time, thus displaying them on the chart as if they were tracing out the underlying SSC.

After experimental evaluation of several possible models of QT adaptation lag, with knowledge of the two-time constant characteristic of QT adaptation (Franz et al. 1988, Lee et al. 1999) a model of the functional relationship between the dynamic changes in QT with respect to RR emerged.

For any given change in RR, the change in QT is related to the slope of the QT/RR plot at that heart rate. If changes in RR were infinitely slow, the plot would describe the steady state characteristic and the change in QT (ΔQT) due to a change in RR (ΔRR) would be given by the formula:

$\Delta QT = S. \Delta RR$

For more physiological changes in RR, one must incorporate a model for the lag phenomenon. The change in QT comprises an immediate undelayed fraction described as:

$$\alpha(S \cdot \Delta RR)$$

and the remainder as the fraction:

$$(1 - \alpha) \cdot (S \cdot \Delta RR)$$

which has suffered a single pole lag with a time constant of τ seconds. In Laplace transform notation the lag function is thus:

$$\Delta QT(s) = [\, \alpha + (1 - \alpha) / (1 + s\tau) \,] \cdot S \cdot \Delta RR(s)$$

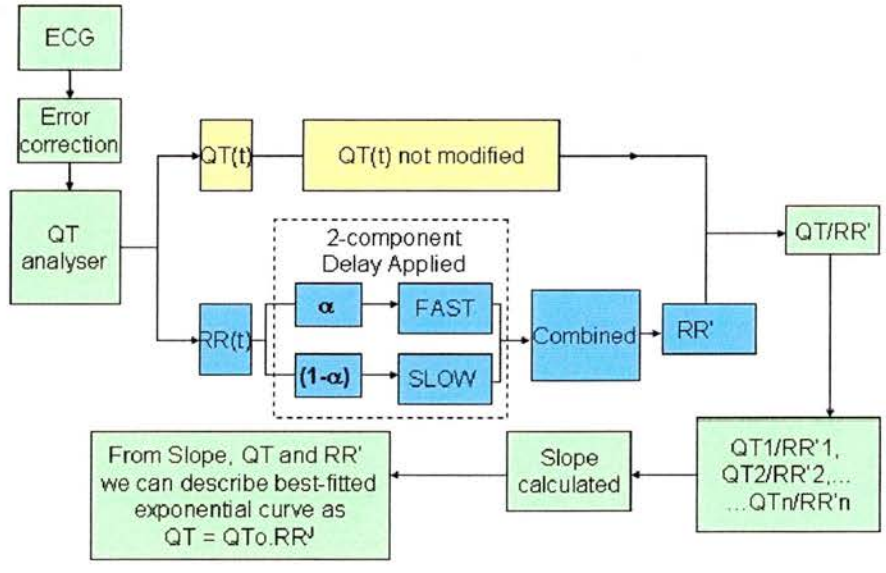
This model was refined electronically by adjusting the time constants and applying the same lag function to the RR signal to create RR', an identically laging version of the RR signal.

From analysis of recordings from 40 normal individuals, it was found that α remained relatively constant throughout the 24h period, with a population range of 0.15 – 0.30. When the time constants of the lag function are correctly adjusted, the QT/RR plot no longer has hysteresis loops but traces out a curve which is presumed to be the

underlying steady state characteristic. Technically however this is now a QT/RR' plot as the QT data is the same but the RR data has been delayed by applying the lag function and is thus labelled RR'. The QT lag compensation is represented diagrammatically in figure 3.3. An example of the QT lag compensation is shown graphically in figure 3.4.

Figure 3.3: Diagrammatic Representation of the QT analyser's functions.

Raw ECG interval data enters the QT analyser, and the QT interval data passes untreated, while the RR data is delayed according to the application of the two component lag (blue boxes), which realigns the delayed RR data (RR') with the undelayed QT data to allow estimation of the QT/RR relationship (QT/RR').



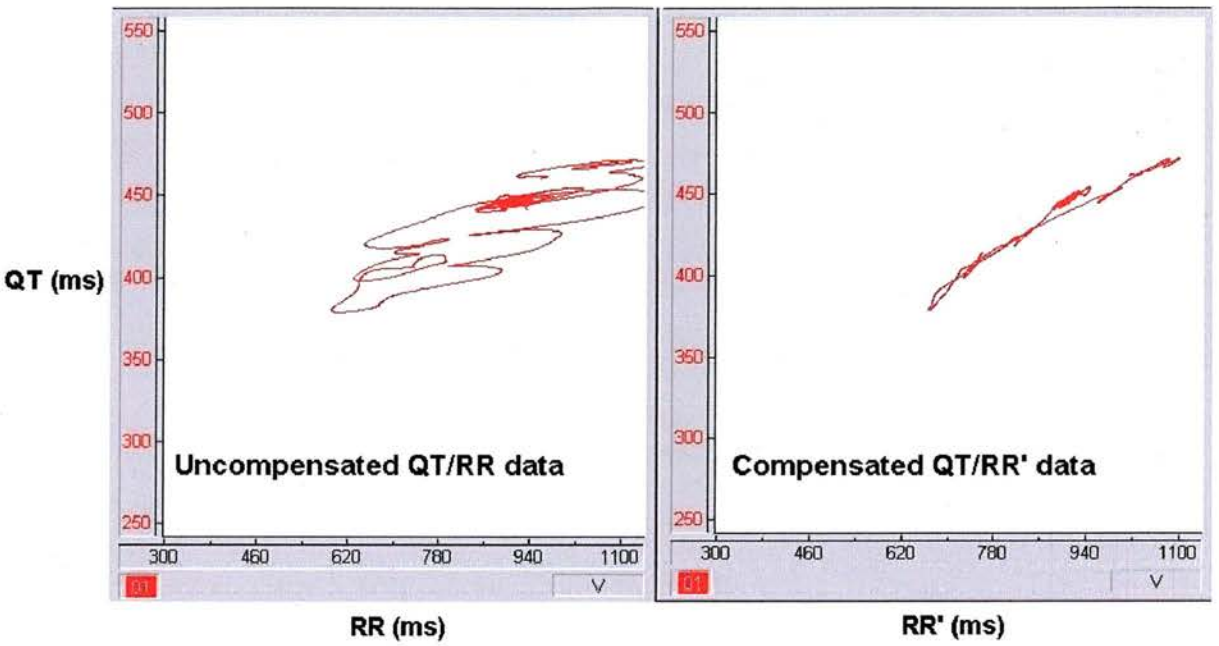


Figure 3.4

An example of the QT lag compensation model in action.

The QT/RR plots contain approximately 3 minutes of QT data. The left panel is a plot of QT against the preceding RR interval. Several loops are visible as the heart rate speeds up and slows down due to the presence of QT adaptation lag. The right panel contains the same QT intervals but they have been plotted against the lag compensated RR (RR'). The hysteresis loops are no longer present and the plot demonstrates a curve.

As these 'pseudo-steady-state' plots are not linear but curved, the relationship is estimated by fitting the data against a general exponential formula with an X/Y intercept at zero. The curve can be described in terms of two variables- the exponent J and QTo which is the QT interval at RRo, a reference RR interval (chosen as 1000ms for reasons of convention).

3.4.3 Continuous Assessment of the QT/RR' Relationship

Having established the relative proportion of alpha for each recording, the QT and RR' intervals are replayed and continuously cross correlated against one another within a continuously scrolling time window, the duration of which can be varied. In this thesis, the window is of five minutes duration unless otherwise stated. A continuous estimate of the cross correlation coefficient is derived. Data are only used when the correlation at that time is greater than 0.8. Low correlations generally occur during noisy segments of recording or when the analyser is unable to determine T_{end} correctly due to a change in morphology or amplitude. The slope of the steady state characteristic is continuously calculated as the linear regression coefficient within the window and used to further define the underlying characteristic.

The assumption is made that the curve conforms to the general formula:

$$\mathbf{QT = QTo\ (RR'/RRo)^{J}}$$

This formula is of the same form as those derived by Bazett ($QT = QTc \cdot RR^{0.5}$), and Fridericia ($QT = QTc \cdot RR^{0.333}$), although these formulae were derived largely from grouped data, mainly in the resting state and it is unclear whether subjects had been in a resting state for any length of time (the stabilisation time of the QT interval was unrecognised in that era).

For equations of the general formula, only one curve can pass through a given point (RR'1,QT1) with slope S. The exponent describing this curve can be shown to derive mathematically from:

$$\mathbf{J = S \cdot (RR'/QT)}$$

In a dynamic situation with non-steady state data, when RR', QT and S are all varying continuously, J is also varying. The QT/RR relationship can therefore be continuously calculated over the scrolling time window with the formula:

$$\mathbf{QTo\ (t) = QT(t) \cdot (RR(t) / RRo)^{J}}$$

The analysis will therefore generate continuous outputs of RR'(t), QT(t), S(t), J(t) and QTo(t) which are plotted as trends for the duration of the recording.
Recordings can therefore be analysed to give mean values of the entire recording, selected segments, or trend data over segments.

3.5 Conclusions

This approach offers a significant advantage over existing methods which result in a greater loss of data and/or underestimation of the QT/RR relationship due to hysteresis. The description of the QT/RR relationship in terms of the two variables QTo and J will determine a unique curve for those values, allowing the graphical description of QT over the entire physiological range of heart rates at that point in time.

When heart rate changes dramatically such as on sustained exercise, it is generally accompanied by changes in autonomic tone, posture, body temperature and circulating catecholamines. In these circumstances, it is then not generally acceptable to extrapolate to say what the QT interval would be at 50 beats per minute, but it is possible to say that the relationship has changed. In this case, the graphical representation of the curves is often more helpful that quoting a value of QTo and J.

Chapter 4

The impact of QT Lag Compensation on Dynamic Assessment of Ventricular Repolarisation: Long-term reproducibility and the impact of lead selection

4.1 Introduction

In previous chapters we have discussed the various factors influencing the QT interval, the numerous methods for correcting QT interval for heart rate and the reasons why none of these may be suitable. In the last chapter we discussed the Neilson method for the dynamic assessment of the QT/RR relationship from Holter recordings. In the previous sections, we discussed the likely effect of QT hysteresis on the estimation of QTc from non-steady state data. Here we present data which demonstrate the difference in the estimation of the QT/RR relationship from Holter data in healthy volunteers.

In order for any test to be reliable, it is essential that it is reproducible so that any observed differences cannot be dismissed as being due to natural variation in the parameter being assessed .In addition, it is important that we are aware of the impact of other potential variables which in the case of Holter recordings for QT analysis, could include the use of one or other channel for the analysis.

4.2 Hypotheses

The primary hypothesis was that due to the QT adaptation lag, continuous assessment of the QT/RR relationship would lead to underestimation of the slope and shape of the QT/RR curves. The secondary aims were to establish the reproducibility of the method and the impact of using different leads.

4.3 Method

Fifteen healthy male volunteers (mean age 28) without a cardiac history and on no medication underwent 24 hour ECG recordings using 2 channel 'Tracker 2' recorders (Reynolds Medical, Hertford, England) on two occasions one week apart. Standard bipolar thoracic leads CM5 and CM1 were used. All subjects were asked to abstain from alcohol and follow their normal daily routines on both recording days. One subject was excluded from further analysis due to the presence of frequent supraventricular ectopics. Consent was obtained in all subjects in accordance with our local ethics committee requirements.

The tapes were replayed on a Pathfinder Analyser (Reynolds Medical Limited, Hertford England) which excluded ectopic complexes and those which were significantly distorted by artefact. The analyser measured each RR interval and its associated QT interval. The T_{end} was measured using the slope method whereby the end of the T wave is determined as being the point at which the current slope of the T wave drops below a pre-determined proportion of the maximum slope. The accuracy of the automated QT interval measurement has been validated independently (Lande et al. 2000).

Twenty four hour files of RR and QT intervals are then processed on a personal computer using a novel technique to determine the QT:RR relationship. The three stage process is described briefly below, but the theoretical aspects have been covered in more detail in chapter 3.

First, the well known two component time lag (Franz et al. 1988, Lee et al. 1999) with which the QT interval follows changes in RR interval is 'compensated' by applying a matching two component time lag to the RR data. This re-synchronises the QT and RR variations so that, when the compensation is correctly adjusted, a screen display of QT against RR no longer shows the characteristic loops due to "QT Hysteresis" but retraces the corresponding part of the underlying 'steady state' QT/RR curve. This is the curve that would have been traced if RR had changed slowly enough so the effect of the QT delay on the plot would be negligible. During analysis the operator can confirm the absence of 'hysteresis loops' and hence correct compensation for the QT lag.

Secondly, throughout the analysis, the RR and QT signals are cross-correlated within a moving five minute time window that is scrolled through the 24-hour data. So long as the correlation between QT and RR remains high ($r > 0.8$), the slope (S) of the QT/RR plot around each successive (RR, QT) point is computed as the best-fitting line in the time window currently centred on that point. Thus a continuously updated measure of the slope of the QT/RR characteristic curve is generated.

Thirdly, it is found that this slope decreases at longer RR intervals, providing evidence that the steady state QT/RR characteristic is curved. To avoid the necessity of reporting the value of RR at each measure of slope, the simple exponential empirical formula used by both Fridericia and Bazett is adopted.

To allow for the known variation in the QT/RR relationship, a formula with variable exponent is used:

$$\mathbf{QT = QTo * (RR/RRo)^J}$$

Here QTo is the intercept of the curve with the ordinate at RRo, a chosen reference RR interval, and J is the exponent determining the shape of the curve. (Bazett's formula assumes that J is constant and equal to 0.5, while the Fridericia formula is equivalent to adopting a fixed value of 0.33 for J) In the present method the value of J is continuously computed from J = S . (RR'/QT) , where RR' is the compensated value of RR.

4.4 Statistical Analysis

Recordings were excluded from statistical analysis if they did not fulfil the following criteria: data used > 90%, pooled 24h QT:RR correlation >0.8, recording duration >18h. A breakdown of the number of recordings available in each channel is given in table 1. Of the 14 pairs of recordings, 13 pairs were of sufficient quality for assessment of 24h reproducibility in one or both channels. When comparing the difference in the calculated QT/RR relationship between compensated and uncompensated data, all analysable channels were used. This produced a total of 35 acquired recordings that were then analysed with and without lag correction and compared by paired t-test. Due to a low yield of high quality recordings in channel 2

(CM1), only 11 tapes were available for comparison of inter-lead differences when quality criteria were applied. Reproducibility of the technique was assessed by calculation of the coefficient of variation (CV) defined as the standard deviation of the mean difference between recordings, divided by the mean of the population and expressed as a percentage. Inter-lead differences were assessed using paired t-tests.

4.5 Results

The mean pooled 24h correlation coefficient was 0.86 for compensated data, implying that throughout the 24 hour period the correlation between QT and RR data was high. This contrasts with the correlation for the uncompensated data ($r = 0.63$). Although the mean pooled correlation for the population is 0.86, for the duration of most of the recordings it is actually much higher, as can be seen in figure 4.1, a 24h chart from a typical normal subject. Figure 4.2 is a further example of the lag compensation in action during a five-minute excerpt of the playback. The left panel shows raw QT and RR data-points whereas the in the right panel, the lag correction has been applied, increasing the correlation between QT and RR.

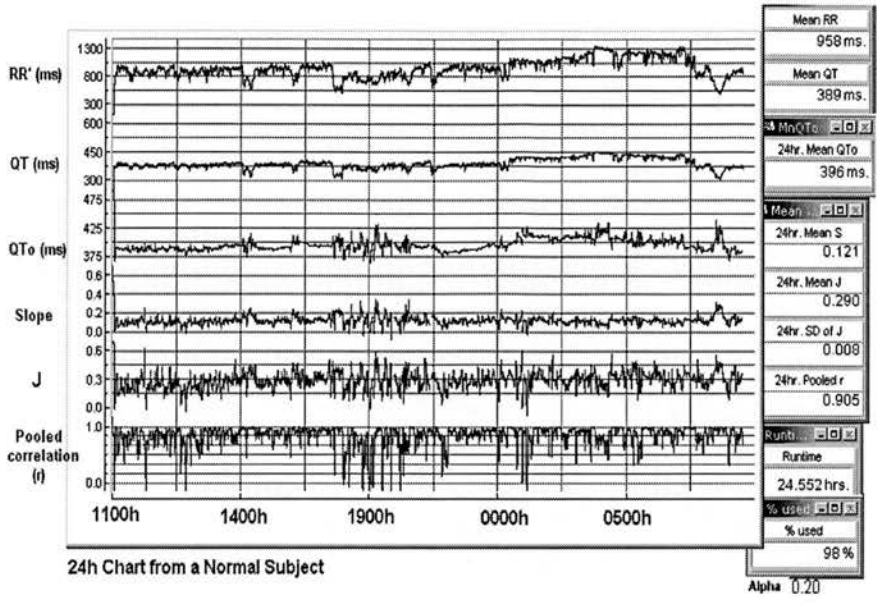


Figure 4.1: A 24h printout of compensated QT and RR (RR'), along with the parameters S and J used to describe the QT/RR relationship. Recording was commenced at 1100h. It can be seen that while the patient is sleeping (0000h – 0730h), there is a slight lengthening of QTo, with reduction in the variation seen during waking hours. Slope is also seen to decrease, secondary to a longer RR interval, meaning the QT intervals are on the flatter portion of the QT/RR curve. There is a slight reduction in J during sleep relative to waking hours. The figures on the right hand side are mean 24h values.

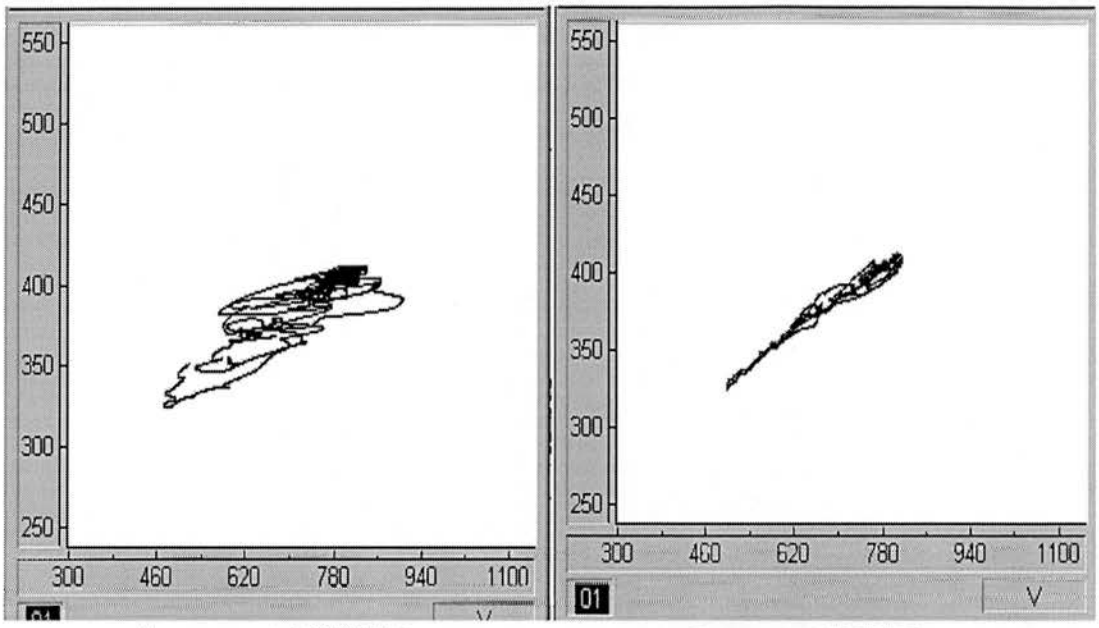


Figure 4.2:

A further example of the QT lag compensation in action. The figure represents a three minute excerpt from a 24h recording. The left panel is raw QT:RR data. Each QT/RR point has been joined to the next by a line. The right panel is the same QT data, but matching lag has been placed on the RR data (RR'). This has resulted in an improved correlation between QT and RR, with accelerations and decelerations in heart rate tracing out one curve. This enables the measurement of the underlying QT/RR relationship as though it were derived from steady state data.

The mean 24h results for compensated and uncompensated values are given in table 4.2. QTo is significantly shorter when data were not compensated. Lack of compensation also results in a reduction in the mean 24h slope which, in turn, reduces the observed 24h mean J. Constructed QT/RR plots using mean 24h compensated and uncompensated results are shown in figure 4.3.

The reproducibility of the method was assessed by comparing mean 24-hour values. Where two channels were of sufficient quality in both recordings, both channels were included in analysis. Table 4.3 gives the mean differences and CV for each of the parameters. The standardised QT at an RR interval of 1000ms (QTo) is highly reproducible despite a 7% variation in mean 24h RR. Slope and J also had a low CV (11% and 7% respectively).

In 11 recordings, both channels were of sufficiently high quality to allow assessment of the impact of lead selection on the value of the parameters. Table 4 details the differences between channel 1 (CM5) and channel 2 (CM1). The slight difference in mean 24h RR is due to automatic editing of noisy segments which differ according to the channel analysed. There was a 15 ms difference in QT and a 13ms difference in QTo between Ch1 and Ch2, with the CM5 lead having a longer mean 24h QT and QTo. CM5 lead also tended to have a steeper slope and higher J.

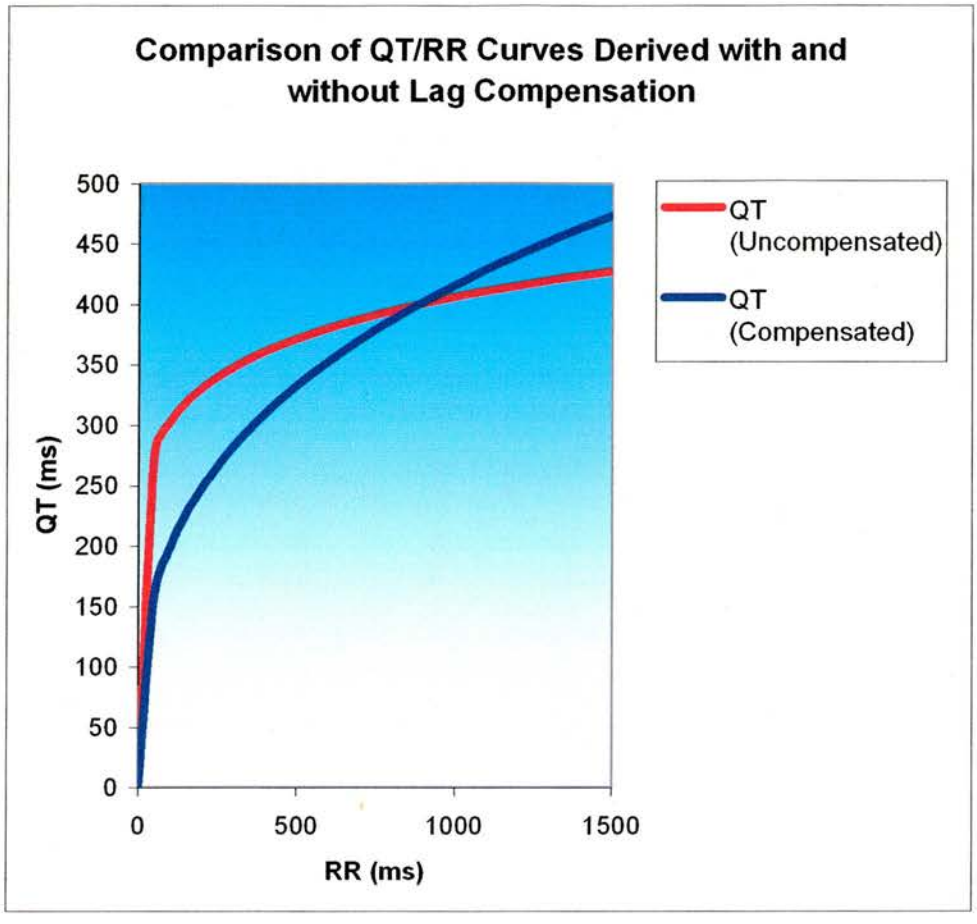


Figure 4.3: Demonstration of the different curves derived by analysing QT/RR data over a scrolling short time frame. The uncompensated data gives a lower value of QTo (red). Mean slope is also lower. The exponent describing the curve (J) is also lower for the uncompensated data. This demonstrates that the continuous assessment of the QT/RR relationship on a beat by beat basis will yield an underestimation of the slope and the rate dependence of the curve.

Summary of Suitability of Recordings for Analysis

	Tape 1	Tape 2	Total of analysable recordings	Pairs where both tape 1and tape 2 analysable in the same channel	Total Pairs (either channel)
Channel 1 (CM5)	12/14	12/14	24/28	11/14	13/28
Channel 2 (CM1)	7/14	4/14	11/28	2/14	
Total analysable recordings	19/28	16/28	35/56		
Pairs where both channel 1 and channel 2 analysable from the same tape	7/14	4/14			
Total Pairs (either tape)	11/28				

Table 4.1: Breakdown of recordings suitable for analysis by channel and tape number. Where the same channel was available for analysis in both recordings (tape 1 and tape 2) this is used as a pair for assessment of the reproducibility. Where both channels were of sufficient quality in the same recording (tape 1 or tape 2), the pair is used to assess the effect of using different leads on mean 24h values. All recordings of sufficient quality, irrespective of channel or tape number, were combined to assess the effect of applying lag compensation on the estimated QT/RR relationship.

Comparison of Lag Compensated versus Uncompensated Data

n=35	RR (ms)	QT (ms)	QTo (ms)	S	J	24h SD of J	24h pooled correlation
Uncompensated	901.4 (86.65)	396 (23.6)	406 (19)	0.06 (0.01)	0.127 (0.019)	0.009 (0.0026)	0.650 (0.08)
Compensated	901.4 (86.65)	396 (23.6)	415.74 (17)	0.146 (0.02)	0.320 (0.04)	0.018 (0.014)	0.87 (0.06)
p value	N/A	N/A	<0.001	<0.001	<0.001	<0.001	<0.00001

Table 4.2:Comparison of lag compensated versus uncompensated ambulatory data. All results are 24 hour means (standard deviation). Correlation between QT and RR is less good when data is uncompensated. There are significant differences in the estimated mean 24h QTo, S and J.

Reproducibility of Parameters for Paired Recordings One Week Apart (Compensated Data)						
n=13	**RR (ms)**	**QT (ms)**	**QTo (ms)**	**S**	**J**	**24h pooled correlation**
Mean (SD)	895.65 (89.61)	396.11 (21.63)	415.9 (17.33)	0.152 0.022	0.33 (0.03)	0.893 (0.044)
Mean difference (SD)	15 (66.63)	5.1 (12.1)	5.0 (8.11)	0.0041 (0.017)	0.00829 (0.025)	-0.012 (0.046)
CV	7.44%	3.04%	1.95%	11.1%	7.42%	5.2%

Table 4.3: Reproducibility of parameters from paired recordings one week apart. The coefficient of variation (CV) is calculated as the standard deviation of the differences between recordings, divided by the mean value for the population x 100% (SD/mean *100%). All values are mean (SD).

Interlead Differences in 24h Parameters (Compensated Data)

n=11	RR (ms)	QT (ms)	QTo (ms)	S	J	24h pooled correlation
Channel 1 (CM5) Mean (SD)	902 (107)	405 (21.2)	424 (14.9)	0.151 (0.03)	0.324 (0.01)	0.89012 (0.03)
Channel 2 (CM1) Mean (SD)	894 (97)	389 (31.3)	409 (19.7)	0.142 (0.026)	0.313 (0.021)	0.83 (0.05)
Mean difference	9.5 (18.02)	15.1 (16.2)	13.2 (16.4)	0.0094 (0.010)	0.0132 (0.019)	0.0663 (0.060)
p value	NS	<0.05	<0.05	<0.05	0.06	<0.05

Table 4.4: Interlead differences in 24h parameters. Paired t-test used to assess the significance of difference between leads. All values are mean (SD).

4.6 Discussion

4.6.1 Lag Compensation

Compensating for QT lag by delaying RR data improves the correlation between QT and RR, as evidenced by the high pooled 24h correlation coefficient. This demonstrates the ability of the method to compensate for hysteresis and enable estimation of the underlying QT/RR relationship using short-term non-steady state data. QT lag compensation also corrects for the underestimation of slope that occurs with beat-by-beat assessment of QT dynamics. Other researchers have shown that when non-steady state data is used, the QT/RR slope is less steep (Badilini et al. 1998).

The use of a short (5 minute) time window offers the possibility of high temporal resolution for assessment of the underlying QT/RR characteristic.

4.6.2 Diurnal Variation

We found that J varies constantly throughout the day, usually within a fairly narrow range, as indicated by the small average 24h standard deviation of J (24h SD of J, table 2). However, occasional peaks and troughs can occur. An example of circadian changes in J can be seen in figure 1. Whether the degree of variation in J, which can be described by the 24h mean SD of J for the recording, reflects the degree and frequency of alteration in factors such as the autonomic nervous system remains to be seen. In contrast, QTo seems to vary little with this method, showing a trend to be longer at night, rather than varying constantly. Again, occasional peaks and troughs are seen in QTo, most commonly on waking in the morning. These changes may

reflect the interaction of numerous physiological factors which are known to affect QT independently of rate, such as posture, autonomic tone and circulating factors such as corticosteroids and catecholamines. The peaks on waking may be linked to the increased incidence of arrhythmias seen in the early hours of the day. Acute arousal events have been shown to be important triggers in the initiation of ventricular arrhythmias in some patients with the congenital long QT syndromes (Ali et al. 2000, Moss 1986).

4.6.3 Inter- and Intra- Subject Variation

Even in this small study, there was a considerable spread of 24h mean values of both QTo and J across the population. The range of mean 24h QTo was from 384ms to 448ms, although this has been accentuated by analysing channels 1 and 2 together. Equally, there was a spread of values for J (0.28 – 0.382).

Despite the constantly changing nature of J, and the range of values seen in both QTo and J across the population, the intra-subject mean 24h values of both are reproducible. The 2% CV in QTo corresponding to an 8ms difference between recordings is small when compared with the observed 17ms SD of QTo across our population. A similarly small difference is seen in J. This suggests that genuine differences exist between individuals, and that the 24h mean QT/RR curve is reproducible under stable conditions. The high reproducibility of this new method suggests that even small intra-subject changes in the QT/RR relationship could be detected.

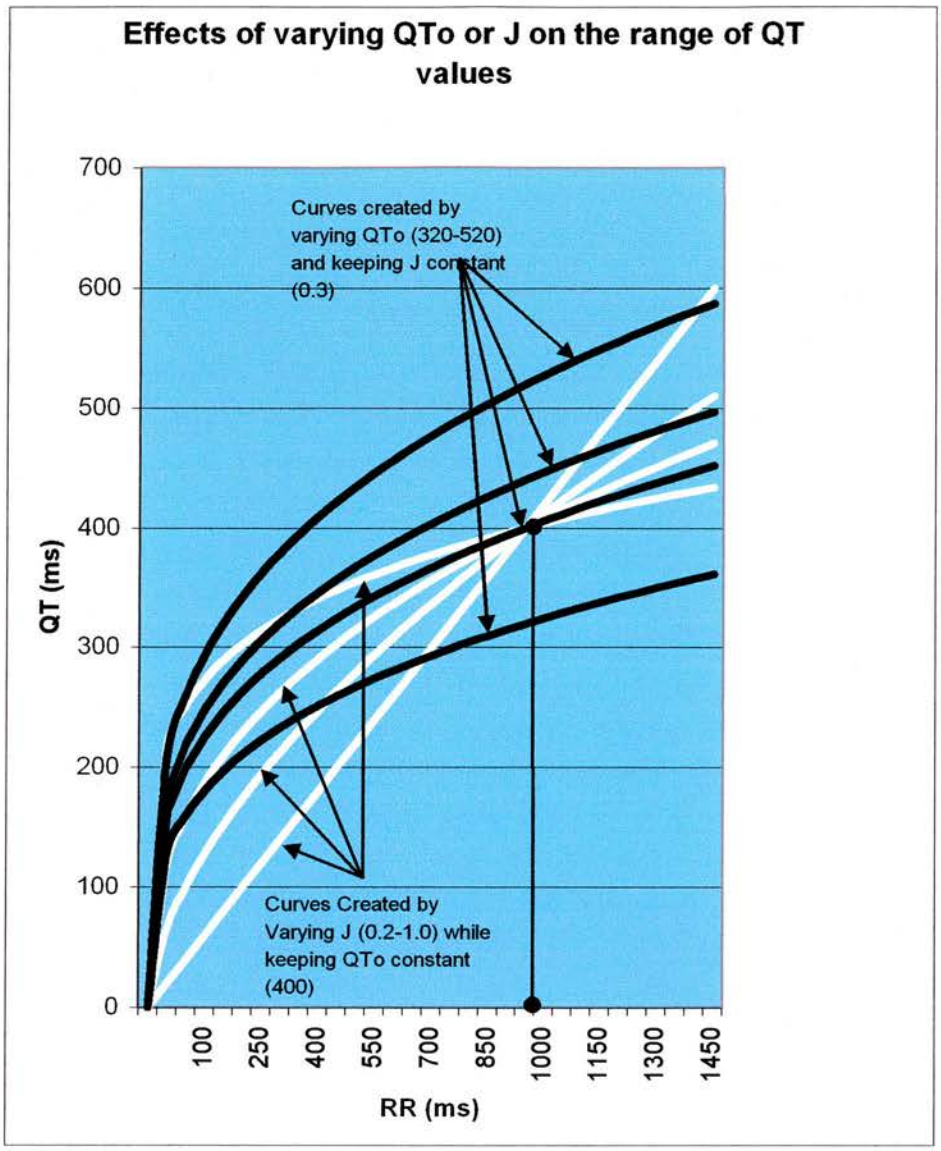


Figure 4.4: Graphical illustration of QT/RR curves with varying values of QTo (black curves) and J (white curves). This is intended to illustrate that both QTo and J influence the QT/RR relationship. Changes in QTo will tend to alter the 'height' of the curve, whereas changes in J will affect the shape (i.e. straightness or curve). From this illustration, it can be seen that the slope, s, which is the tangent to the curve at any individual point will vary according to the position on the curve.

4.6.4 Implications for Rate Correction Formulae

The variation of J with time and among subjects highlights the problems associated with the search for a universally applicable rate correction formula, as discussed by others (Hnatkova and Malik 1999). Figure 4.4 is a constructed plot of families of curves created by varying either QTo or J. It can be seen that as QTo or J varies, significant differences in QT occur over a range of heart rates. It can be seen that under certain circumstances, a 'normal' QTo at a standardised heart rate of 60 beats per minute can be associated with very abnormal QT intervals at fast or slow heart rates if J is significantly different from 'normal'. By describing the QT/RR relationship in terms of both QTo and J, a more informed judgement can be made as to whether the QT/RR relationship is abnormal.

4.6.5 Significance of Lead Selection

Lead selection has been shown in this study to produce a small but significant difference in observed QT and QTo. There is also a small absolute difference in estimated values of S (0.01) and J (0.01). Estimation of the spatial dispersion of repolarisation by measurement of the QT dispersion has generated a huge number of publications over the years. Controversy exists over whether the measured dispersion in QT intervals is truly a reflection of spatial differences in repolarisation or whether it is due the geometrical projection of the T wave on the ECG (Lee et al. 1998, Kors and van Herpen and Van Bemmel 1999) and there have been numerous editorials on the use and significance of QT dispersion. These recent editorials have questioned the significance of QT dispersion (Malik 2000, Coumel and Maison-Blanche and Badilini

1998, Sahu et al. 2000) and one even dubbed it the 'greatest fallacy in electrocardiography in the 1990's (Rautaharju 1999). Whether QT dispersion is real or not, the significance of lead differences in the context of analysis of the QT/RR relationship is unknown. From a technical standpoint, the use of a standardised lead with a low amplitude T wave and an unfavourable signal to noise (S/N) ratio is more likely to provide erroneous results than selecting the lead with the most accurately determinable T_{end}, even if it lies on a different axis.

4.7 Limitations

This study was relatively small and examined only normal subjects. Further work would be required to establish normal ranges and the influence of gender. As with all methods for the analysis of QT dynamics from ambulatory recordings, the quality of acquired ECG waveforms, both in terms of signal quality and the accurate editing out of frequent premature or aberrant beats, is essential. T wave morphology may be abnormal or of low amplitude in many patients with heart disease and ectopy more frequent. This will affect the yield of recordings of sufficiently high quality where accurate T_{end} measurement is possible. In this study, mean 24h values are quoted and an average of 72,000 beats was analysed per recording. A few non-edited abnormal beats are unlikely to influence results. The yield of high quality recordings in this population was good, particularly for the CM5 channel. Individuals were young, slim and had normal hearts with normal T wave morphology. This is often not the case in clinical practice. It can readily be seen that when analysing CM1, T waves were of lower amplitude, degrading the S/N ratio so that when our selection criteria are

applied, the yield drops from more than 90% to less than 50% of recordings suitable for analysis. This finding reinforces the importance of ranking a good T wave morphology over lead position when selecting electrode sites for ECG recordings intended for QT analysis.

4.8 Conclusions

This method shows potential for the assessment of both the short and long term characteristics of the QT/RR relationship in healthy volunteers. It represents a significant change from previous approaches to the analysis of dynamic recordings in that it is the first to employ a method for compensating for QT lag. As the QT/RR relationship appears to follow a curve over a broad range of heart rates in ambulatory data, the QT/RR characteristic is described in terms of an exponential formula with two variables, QTo and the exponent J. It removes the need for quoting a slope for variations in the RR interval. It may be well suited to the assessment of the effect of medications on aspects of ventricular repolarisation. Further work is required to establish normal values in a larger population and to evaluate differences under non-physiological circumstances.

Chapter 5

Assessment of Repolarisation Dynamics in Patients with Heart Failure: Correlation with Functional Class

5.1 Introduction

Heart failure is a clinical syndrome due to impaired heart muscle function, with subsequent changes in neurohumoral activation, fluid retention and shortness of breath. It can be a primary disorder due to myocardial disease or can occur as the end result of a long list of conditions which can result in failure of the heart to maintain the circulatory requirements of the body. To an extent, the final pathway is the same in that chronic pressure overload in the ventricle results in dilatation of one or both ventricles with impairment of contractile function. At a histological level, there is an increase in myocardial fibrosis and the individual myocytes are hypertrophied in response to activation of the sympathetic nervous system and the release of growth factors.

In the western world, the commonest cause of heart failure is ischaemic heart disease, with previous myocardial infarction or chronic ischemia. Valvular heart disease is also a major cause, and can be divided into two groups- those with pressure overload (such as aortic or mitral stenosis) and those with volume overload as a consequence of valvular regurgitation (mitral or aortic regurgitation).

5.2 Epidemiology and Prognosis

Congestive Cardiac Failure (CCF) is a common condition, with an estimated 2 million patients in the United States with the condition, with an estimated 900,000 hospital admissions per year due to CCF. Mortality rates are as high as 50% per year in some studies and 200,000 people die annually from CHF. Despite recent advances

in medical therapy, the mortality remains high. The natural history of the disease is a gradual progression in haemodynamic dysfunction with worsening symptoms and ultimately death due to a failure of the circulation to maintain other organ systems.

However, many of these patients die suddenly and unexpectedly (Kannel and Plehn and Cupples 1988) and in many cases, ventricular tachyarrhythmias are responsible (Luu et al. 1989, Wilber et al. 1974, Roberts 1986). Sudden cardiac death may even occur in those patients with less severe disease, and some studies have suggested that those with less severe disease, in relative terms are more likely to die suddenly than those in the worst functional classes. In one series of unexpected in-hospital cardiac arrests in patients with NYHA class III or IV HF, 15 of 29 cases of sudden death were due to ventricular tachycardia (VT) or fibrillation (VF) (Stevenson et al. 1993).

Macroreentry is one mechanism by which malignant arrhythmias can arise, in areas where there is slow conduction, such as around the border zones of previous myocardial infarction. This typically results in sustained ventricular tachycardia (VT). However, ventricular fibrillation (VF) without preceding VT is often seen either clinically or at electrophysiological (EP) testing in patients with impaired ventricular function.

5.3 Electrophysiological Changes in the Failing Heart

The failing ventricle is known to exhibit prolongation of action potential duration (APD) compared to those of normal hearts (Beuckelmann and Nabauer and Erdmann

1992, Gwthmey et al. 1987, Vermeulen et al. 1994, Beuckelmann and Nabauer and Erdmann 1993). The prolongation of action potential duration is most probably an apaptive phenomenon to prolong the duration of myocytes contraction to help maximise stroke volume. In animal models this prolongation is progressive with the degree of heart failure, and occurs in the absence of other electrophysiological abnormalities such as changes in resting membrane potential, action potential amplitude or upstroke velocity. The plateau phase of the action potential is quite labile and exquisitely sensitive to small changes in currents, which can lead to changes in the duration of repolarisation. Reductions in serum potassium can further lengthen the AP and lead to early after-depolarisations (EADs), particularly at low heart rates (de Groot et al. 2000). These after depolarisation can trigger ventricular ectopy or even sustained ventricular arrhythmias.

Studies of the changes in ion currents in heart failure have shown that several abnormalities exist although there is considerable variation between species. In human cells the most consistently reported finding is a reduction in I_{to}. I_{to} is a brief current occurring during phases 0 and 1 of the action potential. Although brief, its down regulation by factors such as α-adrenergic stimulation will affect the level of the plateau, therefore influencing the magnitude of all the currents responsible for repolarisation.

Down-regulation of inward potassium mediated currents (an efflux of potassium from the cell resulting in net repolarisation) has also been noted in human tissue but the results are less consistent than the finding of reduced I_{to}. Certainly, these inward

currents are responsible for the prolonged plateau phase and reduction in these currents increases the propensity to the development of arrhythmogenic EADs.

Intracellular calcium handling is also abnormal in heart failure and is thought to account for the prolongation of relaxation and impaired frequency dependent facilitation of contraction. Ventricular myocytes from failing hearts show a reduced density of current mediated through the L-type calcium channels. There is also a reduced augmentation in the current in response to adrenergic stimulation which would normally increase the force of contraction. The rate related potentiation in I_{CaL} is also attenuated. All of these changes in ion currents will produce a prolongation of action potential duration and a reduction in excitation contraction coupling.

5.4 Hypotheses

Although extrapolation from cellular studies across species is not ideal, prolongation in APD and QT is certainly present in failing human hearts and these changes may predispose the subjects to triggered activity and the initiation and maintenance of malignant rhythms. To allow comparisons of QT duration between individuals and populations, it is necessary to correct the QT duration for heart rate, as this is the greatest single influence upon QT. However, autonomic tone and the effects of many cardiac drugs may also influence QT duration. As discussed in the previous chapters, correcting QT for rate is problematic and has led to the development of numerous formulae of linear, logarithmic and exponential type, although recently researchers

have concluded that no single formula is universally applicable (Hnatkova and Malik 1999).

This chapter examines the repolarisation dynamics of patients with heart failure versus healthy volunteers using the method of Neilson as described in the previous chapters. Our hypotheses were that in light of the evidence of membrane current and action potential abnormalities in patients with heart failure it is likely that they will also exhibit abnormalities of repolarisation. The rate dependence of the QT interval may also be abnormal in heart failure given that many of the currents responsible for the action potential are also rate dependent. If this is the case then the abnormal rate dependence will have serious implications for any method to correct QT for heart rate, whether from resting ECGs or ambulatory data. A secondary hypothesis was that the degree of any observed abnormalities may correlate with the severity of heart failure.

As discussed in chapter 1, previous methods for analysis of ambulatory recordings have been limited through methodology in the continuous assessment of the QT/RR relationship, relying on averaging of long segments or steady state periods to produce a reliable result. In addition, the QT/RR relationship is often quoted in terms of rate dependent variables such as slope. Using Neilson's method we again quote results in terms of mean 24h QTo and 24h mean J.

5.5 Methods

5.5.1 Patient Population and Data Acquisition

Patients with ischaemic heart disease and either symptoms of heart failure or left ventricular impairment (or both) who had been stable on cardiac medications for at least one month were suitable for inclusion in the study. Left-ventricular ejection fraction was estimated by echocardiographic, radionucleide or angiographic methods, and patients were divided into broad groups according to the severity of impairment (severe = EF<15%, moderate = 16-25%, mild = 26-40%, and near normal = EF >40%). Patients on agents known to prolong the QT interval were excluded, as were all patients with bundle branch block (BBB) or atrial fibrillation (AF). Data from recordings in 41 patients from NYHA class I – IV were compared with 15 age matched healthy volunteers. NYHA functional class was assessed by a clinician (ADF) blinded to the results of the ambulatory ECG data. The characteristics of patients and controls are shown in table 5.1, and the characteristics of the CHF group are presented in table 5.2 by NYHA class. Twenty-four hour ambulatory ECG recordings were acquired with Tracker recorders (Reynolds Medical, Hertford, England) with standard bipolar thoracic leads CM1 and CM5.

Table 5.1: Characteristics of subjects. Data are expressed as means (SD), or as percentages.

	Healthy Volunteers	CHF
Age	53 (6)	57 (14)
Sex	10 male	35 male
EF	Not assessed	25% (14)
Mean heart rate (SD)	71 (6)	70 (11)
Beta blockers	N/A	50%
ACE Inhibitors/A2 antagonists	N/A	90%
Diuretics	N/A	90%
Digoxin	N/A	5%
Class III agents	N/A	0%

Table 5. 2: Breakdown of patient characteristics by NYHA class. These data highlight the importance of factors other than ejection fraction which determine symptoms, such as obesity, hypertension and diastolic dysfunction.

	NYHA 1 (n= 6)	NYHA 2 (n=22)	NYHA 3 (n=12)	NYHA 4 (n=4)
Ejection Fraction	36% (14)	24% (14)	29% (12)	28% (27)
Beta-blockers	25%	43%	75%	25%
ACEI	75%	87%	100%	75%

5.5.2 Dynamic QT/RR Measurements

The tapes were replayed on a Pathfinder Analyser (Reynolds Medical Limited, Hertford England) which excluded ectopic complexes and those which were significantly distorted by artefact. The analyser measured each RR interval and associated QT interval. The T_{end} was measured using the slope method whereby the end of the T wave is determined as being the point at which the current slope of the T wave drops below a pre-determined proportion of the maximum slope. The 24h QT/RR relationship is calculated using the method described in the previous chapters.

5.5.3 Statistical Analysis

To minimise the impact of noisy recordings on results, only tapes from subjects where the percentage data analysed was greater than 80% and the mean 24h correlation between QT and RR was greater than 0.7 were included. Mean 24h parameters from Holter recordings were compared between populations by unpaired t-test.

5.6 Results

5.6.1 Characteristics of RR and QT

There was not a significant difference in mean 24h RR or QT between the two groups although there was a trend towards a shorter mean 24h RR interval in the CHF group. The mean 24h QTo was significantly prolonged in the CHF group (461 vs 426ms,

p<0.005). Examples of 24h ambulatory QT/RR data from a control and a healthy volunteer is shown in figure 5.1.

5.6.2 Rate Dependence of the QT/RR Relationship

The mean 24h slope (S) was also steeper in CHF (0.195 vs 0.140, $p < 0.01$). The mean 24h J (the exponent of the general formula that determines the form of the QT/RR curve) was significantly elevated in CHF (0.38 vs 0.28). In contrast to the slope, J is independent of heart rate.

Table 5.3: Characteristics of 24h recordings. Data expressed as mean 24h values (SD)

	RR (ms)	QT (ms)	QTo (ms)	S	J	24h SD of J	Pooled 24h r value
HV (n=15)	845	402	426	0.14	0.28	0.05	0.742
	(105)	(24)	(20)	(0.02)	(0.05)	(0.05)	(0.08)
CHF (n=41)	859	420	461	0.20	0.38	0.181	0.77
	(152)	(45)	(37)	(0.07)	(0.11)	(0.25)	(0.10)
p value	**0.76**	**0.18**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**0.25**

Constructed QT/RR curves created by using the mean population values of QTo and J are shown in figure 5.2 to illustrate the different characteristics over a range of heart rates.

5.6.3 Variation in the QT/RR Relationship

The spread of values of J throughout the 24h period indicated by the mean 24h SD of J is much greater in the CHF group (0.181 vs 0.059, $p< 0.01$), reflecting an increased variation in the relationship between QT and heart rate. This data is summarised in table 5.4. The increased variation in J cannot be explained by differences in the lag compensation as the overall correlation between QT and RR for compensated data is comparable between the two groups, as indicated by the similar pooled mean 24h correlation (r).

5.6.4: Correlation with the degree of symptoms or severity of LV Impairment

When the CHF group is sub-divided according to NYHA class, the values of S, QTo and J increase with worsening functional class (figure 5.3). Analysis of variance (ANOVA) confirmed statistical significance (table 5.4). In contrast, when patients were sub-grouped according to ejection fraction (0-15%, 16-25%, 25-40% and >40%), no significant difference is seen between the subgroups (figures 5.4).

Table 5.4: Statistical analysis of NYHA and EF subgroups by analysis of variance (ANOVA). In this table, p values are shown for each parameter measured, according to whether patients were sub-grouped according to NYHA class or ejection fraction.

	NYHA	**EF**
RR	0.17	<0.05
QT	0.11	0.09
QTo	<0.05	0.89
S	<0.005	0.66
J	<0.01	0.83
24h SD of J	0.11	0.59

Figure 5.2: Curves generated from the mean population data in heart failure and healthy subjects. This illustrates how at higher heart rates, little difference is observed between HF subjects and HV subjects. However, at lower rates, the combination of a higher J and longer QTo leads to a separation of the two curves.

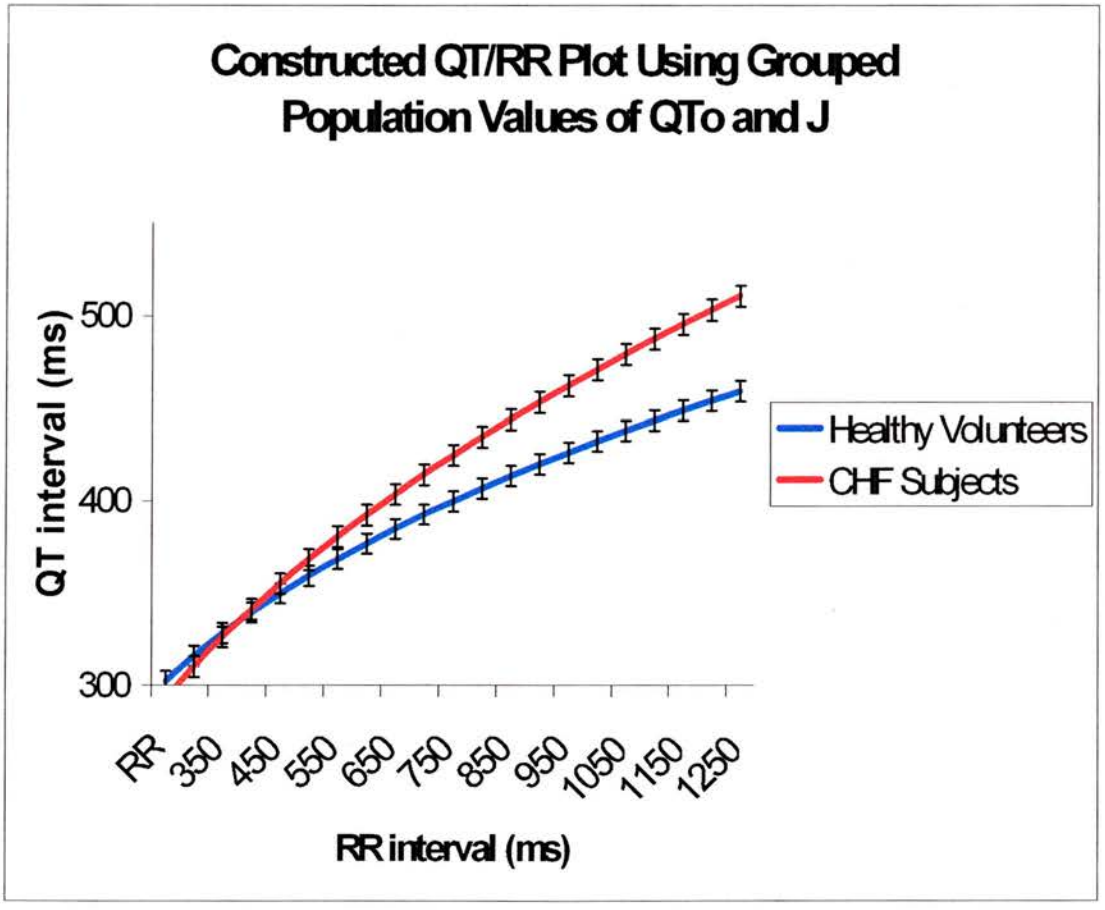
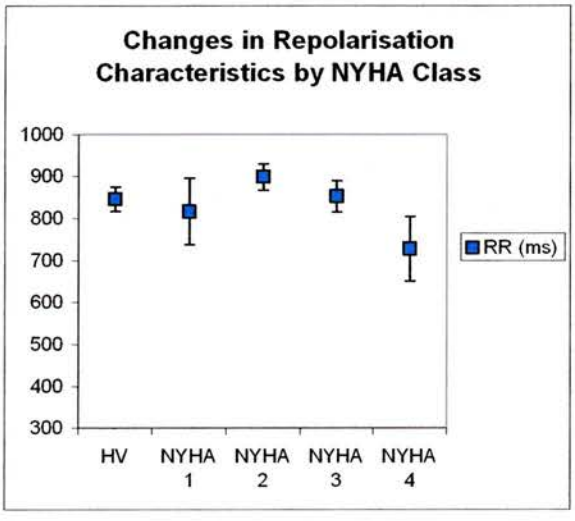
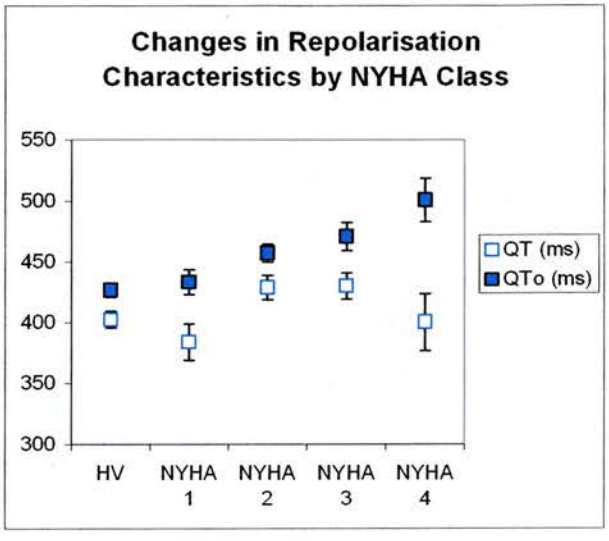
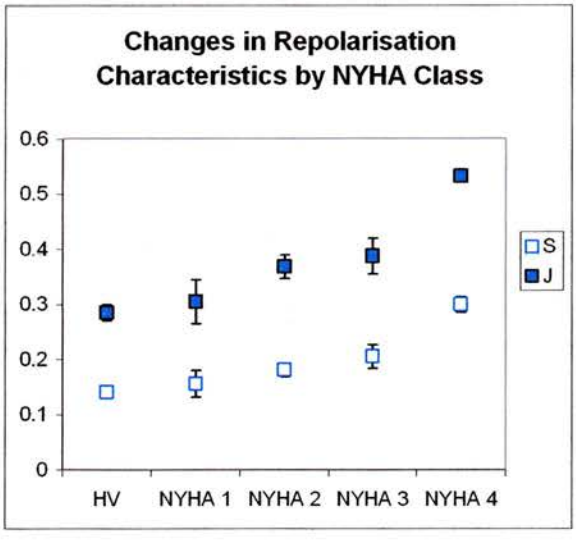


Figure 5.3: Comparison of the correlation between functional class and repolarisation characteristics. Error bars indicate standard errors of the means.







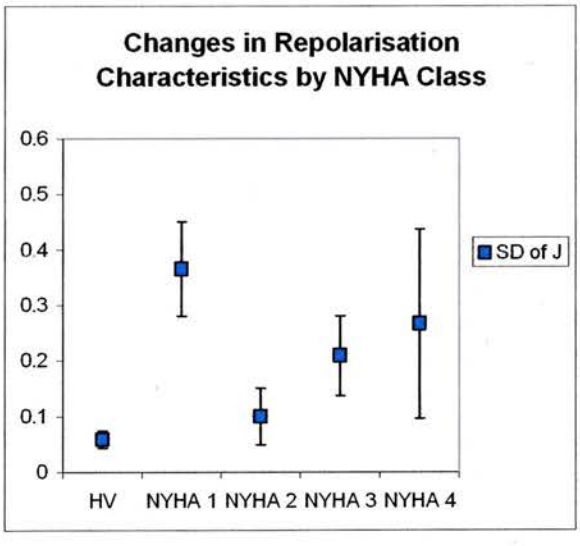
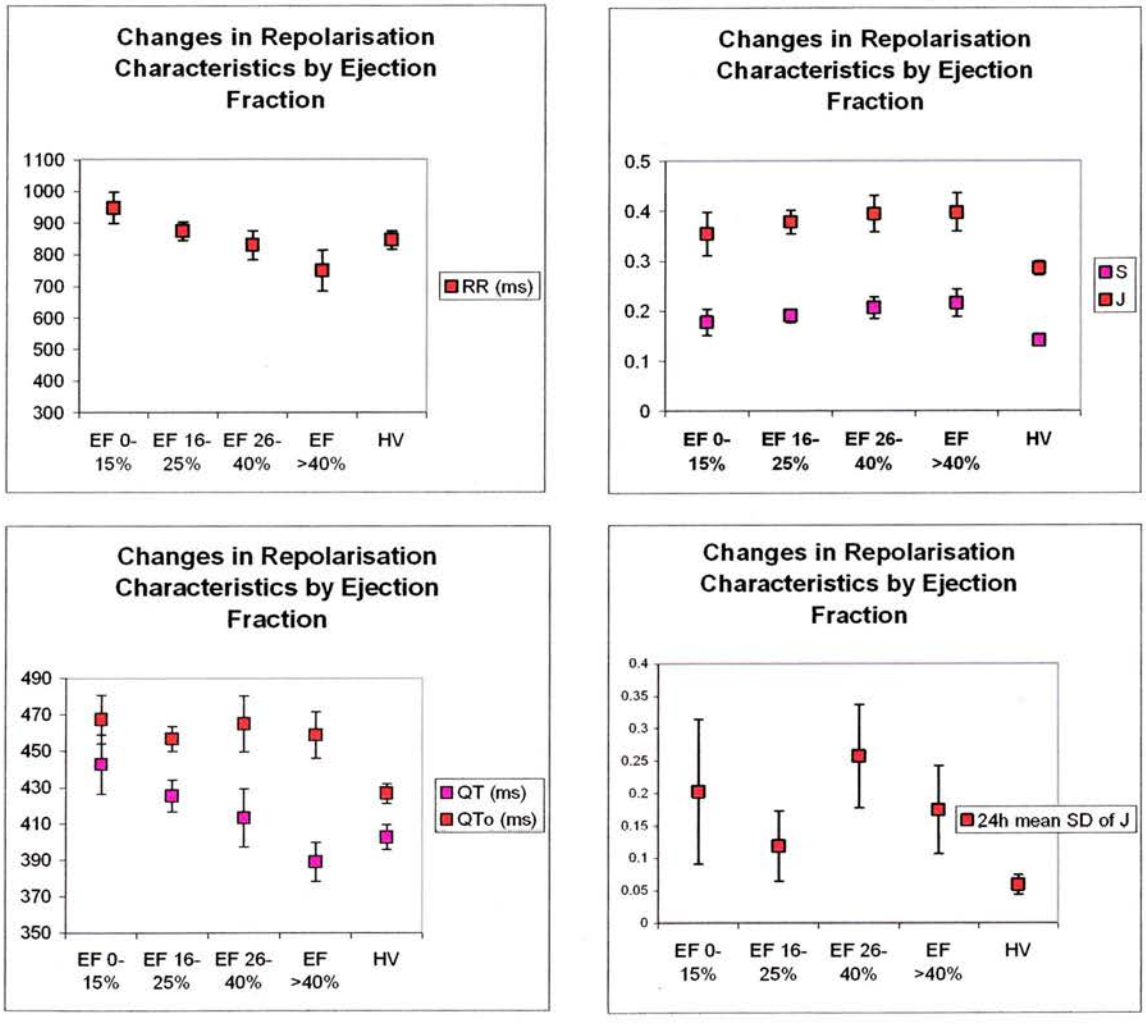


Figure 5.4: Comparison of the correlation between ejection fraction and repolarisation characteristics. Points are mean 24h values. Error bars indicate standard errors of the means.



5.7 Discussion

There is much debate over the best method for the assessment of ventricular repolarisation characteristics. The simplest approach would be to take a resting 12 lead ECG and use one of the available correction formulae to correct for differences is heart rate. Unfortunately, the use of formulae to correct for heart rate are limited by the fact that they assume and impose the same underlying QT/RR relationship on both population groups. Investigators have shown that different subjects have different overall QT/RR relationships, and patients with previous myocardial infarction (Homs et al. 1997) and cardiac arrest survivors (Yi et al. 1999) have steeper QT/RR slopes and longer QT intervals, making direct comparison between populations using the same correction formula at best erroneous, and at worst meaningless. These methods however assume a linear relationship between QT and RR and used grouped data to establish values. Using ambulatory data, the opportunity arises to take long periods of ECG data and from this compute the overall QT/RR relationship, allowing comparison of the QT/RR relationship between groups. This again demonstrates significant differences between patients with heart disease and those without. Unfortunately, most methods do not lend themselves well to the assessment of short-term changes or variability in the QT/RR relationship.

Using this method, it has been possible to assess the 24h relationship in patients with heart failure and healthy subjects. Several differences have become apparent.

5.7.1 24h Characteristics of the QT/RR Relationship

In this study we have demonstrated that with continuous assessment of QT and lag corrected RR, it is possible to describe the relationship between QT and RR in terms of a variable exponential formula with two variables, QTo and J. Figure 5.1 is an example of 24h printouts from a healthy volunteer and a patient with heart failure. In the figure, the values for QTo do not vary dramatically during the day, although there is a slight prolongation at night. J, the exponent of the general formula, is seen to vary constantly throughout the day and night, although generally around a fairly stable mean value. This is in contrast to slope which is lower at higher RR intervals, confirming that the QT/RR characteristic is curved rather than linear.

5.7.2 Differences in the QT/RR Relationship between Heart Failure Subjects and Controls

Although no significant difference was seen between mean 24h RR or QT in these groups, the HF group had a slightly higher mean 24h heart rate (shorter RR) and a slightly longer mean 24h QT. When the overall QT/RR characteristic is established by fitting the data continuously against the general formula, a marked difference emerges between the two groups. The extrapolated QTo (QT at an RR interval of 1s) is significantly prolonged, and the exponent J is greater. The resultant effect of these two abnormalities is that the curves are separated over a broad range of heart rates, with the differences most marked at low heart rates. The steeper curve means that the rate dependence of QT is greater in heart failure.

The ability to detect prolongation of QT is dependent on the method employed for correction of rate related changes. Previous studies have shown that survivors of out of hospital cardiac arrests can have a normal QTc when traditional rate correction formulae are applied, but abnormal rate dependence when QT/RR plots are constructed with raw data (Fei et al. 1994). This is an important point, as if one considers that in this study RRo is chosen arbitrarily as one second for no reason other than convention, it can be seen from figure 5.2 that if RRo was set at, for example, 300ms, little difference would be observed between the groups. QTo as a stand alone measure of repolarisation may show differences between populations, but when combined with the exponent J it takes on a much more useful role, as it allows description of the entire QT/RR characteristic, irrespective of heart rate. Knowledge of both of these variables allows us to more usefully describe repolarisation properties at any point in time, and at any heart rate.

Prolongation of repolarisation has been recognised in animal models of heart failure, irrespective of whether pressure overload, genetic or pacing models are studied. In all models, including human hearts, abnormalities of inward repolarising currents are present, the most consistent being a reduction in Ito, but also reductions in the inward rectifier potassium current (I_{K1}). The net result of a reduction in these currents is to prolong the plateau phase of repolarisation, increasing the possibility of after-depolarisation mediated triggered activity. This will, on the surface ECG, be manifest as a prolongation of the QT interval.

5.7.3 Increased Variability in the QT/RR Relationship

By calculating the mean 24h standard deviation of J, information is obtained about the frequency and magnitude of changes occurring in the QT/RR characteristic throughout the day. In both healthy volunteers and CHF variation is seen, although the magnitude of this variation is greater in heart failure. This increased variation in the QT/RR relationship bears similarities with the study of Berger et al (Berger et al. 1997) as discussed in chapter 2. They employed a novel approach to the assessment of repolarisation dynamics that assesses changes in QT with respect to changes in RR over relatively short time periods (256s). When they compared healthy volunteers with heart failure patients they found that there was decreased heart rate variance but an increase in QT variance in the heart failure group. When these two parameters are combined to produce the QT variability index (QTVI) they found that it discriminated between HV and CHF. This increased variability in the QT/RR relationship may reflect an inability of the myocardium to regulate repolarisation for changes in heart rate.

5.7.4 Correlation with NYHA Functional Class

Although this study was small in size, the subjects were distributed across all NYHA functional classes. When subgroups were analysed, it became apparent that the abnormalities of the QT/RR relationship show a worsening trend with functional class. It is felt that NYHA functional class may correlate with the degree of neurohumoral activation in heart failure. The maladaptive mechanisms of increased sympathetic tone, decreased parasympathetic activity and activation of the renin-

angiotensin-aldosterone system (RAAS) are well described and, either directly or indirectly, can influence cardiac repolarisation, with down-regulation of ion currents and abnormal expression of adrenergic receptors. These factors are likely to be partly responsible for the progressive changes in repolarisation dynamics that we have described. Other investigators (Hintze et al. 1998, Singh et al. 1998, Merri et al. 1992) have shown that beta-blockade reduces the slope of the QT/RR relationship in both healthy subjects and patients with heart disease, and this implies that increased sympathetic drive is at least one of the factors responsible for the increases seen in J and QTo relative to controls. However, caution must be exercised when interpreting data from these studies as heart rate will be lower following beta-blockade, and their method measured slopes of linear QT/RR plots. Given that the QT/RR relationship is likely to be non-linear, we cannot interpret slope as being independent of heart rate. This highlights the advantage of measuring the rate independent quantity J in our study.

The fact that previous studies have suggested that sudden death is disproportionately common in relatively asymptomatic patients NYHA class (Merri et al. 1992), our findings would seem to be discordant. However, arrhythmic death is frequently hard to determine as it is often unwitnessed and rhythms undocumented in the community. Certainly, patients with NYHA IV failure are more likely to die from pump failure compared to NYHA I patients, but it would seem that they are also likely to die of arrhythmias. One study of in-hospital deaths in patients with severe heart failure showed a 50% incidence of arrhythmic death where the terminal rhythm was VT/VF

(Stevenson et al. 1993). Although this population is not representative of our ambulatory out-patients, it would imply that arrhythmias are still very likely to occur in severely limited subjects.

5.8 Limitations

As with all techniques for measurement of the QT interval, accurate and consistent measurement of T_{end} is often difficult to obtain. The results obtained are therefore dependent on the quality of the data. Many patients with heart disease have low amplitude T waves with a T_{offset} that is difficult to determine. In this small study, this was not the case as only patients with high quality recordings were included. Ejection fraction was estimated by a combination of techniques in this study. It may be that an ejection fraction measured by ventriculography at the time of cardiac catheterisation may be greater than that meaured by echo in the same patient, and this may lead to an error in the analyses. However, as the patients were placed in broad groups according to the ejection fraction, this error is likely to be minimal.

Patients with cardiac disease are frequently prescribed agents that influence the QT interval, particularly those who have had arrhythmias. In addition, the use of diuretics may influence electrolyte levels causing changes in QT duration. Patients with ischaemic heart disease or heart failure may be taking beta-blockers that will have an effect on the QT/RR relationship, as shown in previous studies (Emori et al. 1997, Hintze et al. 1998, Singh et al. 1998), however, this has generally been shown to reduce the rate dependence of QT on RR. While the abnormalities shown in this

paper are intriguing, further studies are required to establish whether this method can offer any useful prognostic information in cardiac failure with respect to arrhythmic death. In the era of implantable defibrillators and increasing economic pressures, a means to select patients most in need of these devices is required.

Chapter 6

Repolarisation Abnormalities in Hypertrophic Cardiomyopathy

6.1 Introduction

Hypertrophic cardiomyopathy (HCM) is a myocardial disease inherited as an autosomal dominant trait. Numerous mutations in at least nine genes have been identified. All genes thus far identified code for components of the cardiac contractile apparatus, or sarcomere. These abnormal gene products result in altered sarcomere function, for example by altering actin binding, ATP hydrolysis or calcium sensitivity (Sata and Ikebe 1997). In response to the impaired contractility and higher pressures, growth factors are released which result in myocyte hypertrophy and fibrosis. It is hypothesised that myocardial hypertrophy results as a compensatory response to impaired contractile function. The extreme degree of hypertrophy adversely affects other aspects of cardiac physiology and is considered maladaptive.

The prevalence of the disease in the general population is estimated at 0.2% (Maron et al. 1995) Phenotypically the disease is characterised by inappropriate myocardial hypertrophy occurring in the absence of increased pre- or after-load. Although the exaggerated hypertrophy may be concentric and similar to that seen in severe cases of hypertrophy secondary to hypertension or aortic stenosis, it is more commonly asymmetrical affecting predominantly the interventricular septum. Systolic function appears hyperdynamic, although it is becoming increasingly recognised that a 'burnt out' stage may ultimately occur where the left ventricle becomes dilated with thinning of the walls with an appearance similar to dilated cardiomyopathy.

Myocardial hypertrophy may compensate for sarcomeric dysfunction by increasing the numbers and size of the basic contractile elements and by reducing LV cavity size to lower wall tension. Lower LV wall tension and small end-diastolic volumes lead to an apparent hyper-contractile systolic function. Resting ejection fractions are typically normal or high, but stroke volume (SV) remains in the low to normal range.

There are many patho-physiological consequences of LV hypertrophy. LV myocardium has reduced compliance and impaired relaxation leading to diastolic dysfunction, further reducing the stroke volume. Rapid LV ejection along with a smaller LV outflow tract (LVOT) in approximately 25% of cases can lead to systolic anterior motion (SAM) of the mitral valve and dynamic LVOT obstruction.
The increase oxygen demands of the greater muscle mass, in conjunction with small vessel disease, can render the ventricle ischaemic during exercise.

Myocardial bridging of epicardial coronary arteries is not infrequently found in patients with HCM and has been reported to be associated with QT prolongation and sudden cardiac death (Yetman et al. 1998, Mohiddin, Begley and Fananapazir 2000).

6.2 Histological Abnormalities in Hypertrophic Cardiomyopathy

The histological findings in HCM are marked, with disarray of the normally well organised myocardial architecture and hypertrophy of myocytes. There is an increase in fibroblast numbers, extracellular matrix and also considerable small vessel disease.

A large study of post-mortem hearts from patients with hypertrophic cardiomyopathy (Varnava et al. 2000) characterises the histological abnormalities but also demonstrates some interesting associations between the histological findings and one of the least well understood and arguably most serious consequence of the disease- sudden unexpected cardiac death. They conclude in their paper that the myocardial disarray is a primary abnormality due to the mutation in the sarcomeric protein, whereas the fibrosis and small vessel disease appear to be secondary phenomena which are modified by age, left ventricular (LV) mass and sex. They also found that the degree of hypertrophy, both in terms of heart weight and maximum wall thickness has an inverse relationship with age at death, implying that the patients with more hypertrophied hearts were at increased risk of sudden death. This supports the findings of Spirito et al who published a paper which showed that in a long term follow up of a large cohort of patients, the maximum LV wall thickness was an independent predictor of sudden death, particularly if in excess of 30mm (Spirito et al. 2000).

6.3 Sudden Death in Hypertrophic Cardiomyopathy

HCM is a heterogeneous disease with considerable variation in the severity of symptoms and prognosis. Some patients have progressive disease with increasing fibrosis, small vessel disease, atrial distension and worsening symptoms of heart failure due to either diastolic dysfunction in a stiff ventricle or to pressure overload from sub-valvar outflow tract obstruction. Other patients have an indolent course and have little or no progression over decades. Although the clinical course may be

relatively stable over time, a significant proportion of patients will experience unexpected catastrophic events such as cardiac arrest.

Overall, the mortality statistics from studies in tertiary referral centres quote mortality rates of between 3 and 6% per year for HCM related premature death. However, there is felt to be significant referral bias in these studies as patients tend to be referred due to the severity of the disease or relative youthfulness (Maron and Spirito 1993). More unselected population studies suggest a lower mortality of around 0.5 – 1.5% with overall survival similar to that of the general population (Cecchi et al. 1995,Spirito et al. 1989,Kofflard et al. 1993,Maron et al. 1996).

Although the overall mortality statistics do not suggest that the risk of death is great, the fact that many of the patients who die do so suddenly, unexpectedly and often at a young age underlines the need for accurate risk assessment of these subjects. In an investigation into the cause of sudden death of 158 young athletes in the USA, a post mortem diagnosis of HCM was made in 36%. The next largest subgroup was of coronary anomalies in 19% (Maron et al. 1996b). Given that non-sustained ventricular arrhythmias are common in HCM patients on 24h ECG recordings, it is natural to assume that sustained VT or VF accounts for the vast majority of deaths. In fact, there is evidence that sustained rapid supraventricular arrhythmias such as atrial fibrillation or re-entrant SVTs account for at least some and death is probably due to the associated hypotension accompanying high heart rates in many of these patients.

In addition, myocardial ischemia can occur, with subsequent LV dysfunction and/or arrhythmias.

An association between non-sustained ventricular tachycardia (NSVT) and sudden death has been shown (McKenna 1987), although the presence of this on 24 or 48h Holter monitoring is common in these patients and therefore as a prognostic tool lacks specificity and positive predictive power. A later study by Fananapazir proposed that only NSVT with a history of pre-syncope or syncope or easy inducibility of VT or VF at electrophysiological testing were of use in the estimation of risk (Fananapazir et al. 1992). A strong family history of SCD (Maron et al. 1978), and a patient history of syncope or previous cardiac arrest are more predictive in this group, but as HCM is often diagnosed at post-mortem, one cannot always afford to wait for an episode of syncope prior to initiating action as this is an ominous sign. QT dispersion has also been shown to be increased in patients who died suddenly on pre-mortem ECGs(Buja et al. 1993). In the era where identification of the specific genes involved is becoming possible, certain mutations have been identified as being associated with a very high mortality at a young age (Fananapazir and Epstein 1994,Epstein et al. 1992). Severe LVH on echo (Spirito et al. 2000) has been shown to be associated with an increased risk of sudden cardiac death in a large long-term prospective study. The search continues for a better clinically applicable, widely accessible and ideally non-invasive tool for the assessment of arrhythmic risk.

6.4 Cardiac Repolarisation in HCM

Little is known about cardiac repolarisation in HCM. In 1973, Coltart and Meldrum studied the intracellular myocardial action potential in tissue specimens obtained at operation from two patients with HCM (Coltart and Meldrum 1972). They compared the data with action potentials from hearts with secondary hypertrophy. They noted a marked prolongation of the action potential relative to the hypertrophic controls. In addition there was slowing of depolarisation (phase 0) of the action potential. On surface ECG recordings, the QT has also been shown to be prolonged, independently of QRS widening (Martin and Garson Jr and Perry 1994, Dritsas et al. 1992) in children diagnosed with HCM.

In a paper by Atiga et al, evidence of an abnormal coupling between changes in QT and changes in heart rate was shown (Atiga et al. 2000). There also appeared to be an increase in the variability of the QT interval relative to heart rate. These abnormalities were more marked in the sub-groups of patients known to have genetic mutations associated with an increased risk of SCD ($Arg^{403}Gln$) and a survival rate of 50% at the age of 30 years in one study (Epstein et al. 1992).

Cellular electrophysiological studies in animal and human models of hypertrophy have demonstrated that cells from hypertrophic hearts have a prolonged action potential, and this appears to be an adaptive response to the increased pressure loading. This prolongation may be secondary to decreases in the inward currents generated by the efflux of potassium and/or calcium through the membrane ion

channels. Although hypertrophic cardiomyopathy differs from secondary hypertrophy at several levels, it is conceivable that the prolongation of repolarisation in HCM occurs either as a response to the abnormal loading on the ventricle, or that the mutations causing HCM may also be responsible for the electrophysiologic changes.

6.5 Hypotheses

There is very little experimental evidence of abnormalities of the rate dependence of QT in HCM. Given that QT and QTc have been shown to be prolonged by conventional measurement of resting recordings, our hypothesis was that the prolongation in QTo may be associated with an increased value of J, indicative of a steeper QT/RR curve. Incorporating the evidence of increased QT variability from Berger's group, we also hypothesised that there may be a greater spread in the values dictating the QT/RR relationship, and looked for an increase in the 24 hour standard deviation of J relative to controls. We assessed the dynamic characteristics of the QT/RR relationship in sixty patients with non-obstructive HCM (forty male).

6.6 Methods

60 patients (40 male) referred to the National Heart Lung and Blood Institute, (NIH, Bethesda, Maryland, USA)for assessment were recruited. These subjects were either relatives of patients diagnosed with HCM and diagnosed as part of a family screening programme, or were diagnosed by their referring physicians. All HCM patients were asymptomatic (NYHA I) or mildly symptomatic on moderate exertion (NYHA II).

None had evidence of LV outflow obstruction on echocardiography or at cardiac catheterisation. Patients had been off all medication for at least four half lives. None was taking amiodarone. Forty age and sex matched normal subjects from an existing database acted as the control group. All patients and controls underwent 24h ambulatory ECG recordings using 2-channel recording devices. Bipolar thoracic leads CM1 and CM5 were used. 24h ECG recordings were analysed using the best available channel (see section 4.4) Calculation of the 24h QT/RR relationship was performed as described in chapters 3 and 4.

Exclusion criteria were as follows:

1. The presence of bundle branch block or intra-ventricular conduction defects with a QRS duration of > 120ms.
2. Frequent ventricular or supraventricular ectopics (> 5/minute)
3. Atrial fibrillation
4. Holter recordings of poor quality for QT analysis

A total of 29 (50%) of the HCM patients were excluded from further analysis at this stage due to recordings of insufficiently high quality.

Statistical Analysis

HCM and control group data were compared using student's t-test. Statistical significance was defined as a P value < 0.05.

6.7 Results

Baseline characteristics and results of Holter analysis are laid out in table 6.1.

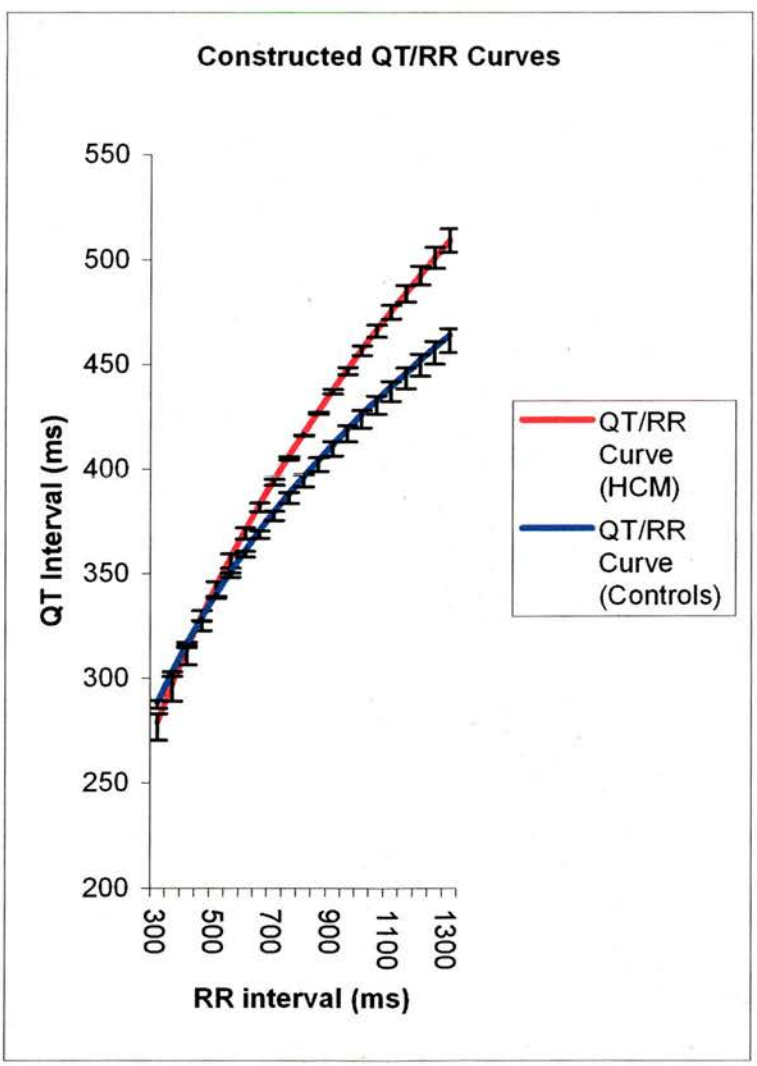
Table 6.1 Baseline characteristics

	Controls n=36	HCM n=31	P-value
Age (years)	39±13	41±10	ns
Female Gender	11	9	ns
RR (ms)	849±105	852 ± 94	ns
QT (ms)	388± 64	420 ± 26	<0.05
QTo (ms)	426± 18	457± 27	<0.0001
Slope	0.16 ±0.03	0.21± 0.05	<0.0001
J	0.32±0.05	0.41± 0.08	<0.0001
24h SD of J	0.03 ± 0.03	0.09 ± 0.14	<0.05
Mean 24h correlation (r)	0.826 ± 0.09	0.87± 0.05	ns

Despite being suitably matched in terms of age, sex and 24h mean RR interval, the HCM group had a significantly prolonged mean 24h QT (420ms vs 388ms, $p<0.05$) and QTo (457ms vs 426ms, $p<0.001$). In the HCM group, slope and J were also significantly increased. Using the grouped population variables QTo and J it is possible to construct mean population QT/RR curves, as shown in figure 6.1. Again, similar to patients with heart failure, the curves are most widely separated at low heart rates.

The mean spread of values of J throughout the 24h period, calculated for each individual as the mean 24h standard deviation of J (24h SD of J), was elevated in the HCM group (0.088 vs 0.033, $p< 0.05$). This increased spread of values was unlikely to have been due to measurement error attributable to noise as the pooled 24h QT-RR correlation coefficient (r) for the HCM population was higher in the HCM group (0.87 vs 0.826).

Figure 6.1: Constructed QT/RR curves using grouped data for the variables QTo and J.



6.8 Discussion

6.8.1 Prolonged Repolarisation and Increased Rate Dependence of QT

The observed differences between these populations have several implications for the assessment of repolarisation dynamics. Firstly, as can be seen in figure 6.1, values of QT are significantly longer throughout most of the physiological range of heart rates, but with more marked prolongation at slow rates. Correcting QT in a dynamic setting using one of the many rate correction formulae for QT (eg Bazett's), imposes the same QT/RR relationship on both populations and therefore would mean an underestimation of QT at most rates in patients, particularly during bradycardias. This prolongation of repolarisation and increased rate dependence is similar to that seen in patients with heart failure, as demonstrated in the previous chapter. To our knowledge, this is the first time that such abnormal rate dependence has been shown in HCM.

Since the discovery of the congenital long QT syndromes, prolongation of repolarisation has been shown to play a role in various cardiac conditions. Potential mechanisms for this altered repolarisation and rate dependence could lie in the cellular handling of calcium. In animal models such as the chronic AV block model in dogs, there is adaptive hypertrophy in response to bradycardia in order to increase the stroke volume and maintain cardiac output. HJ Wellens' group have employed this technique in several projects. After inducing complete atrio-ventricular block in dogs, they are able to monitor the haemodynamic and electrophysiological changes

that take place over time in this in-vivo model. They have demonstrated (Vos et al. 1998) that after 6 weeks of chronic A-V block (CAVB) heart weight increased by more than 50% on average. Action potential was prolonged in both ventricles and surface QT was prolonged compared to acute AV block. It was easier to induce Torsades des Pointes ventricular tachycardia (TdP) in these animals. This was further facilitated by the infusion of the potassium channel blocking agent d-sotalol. In a later article (Sipido et al. 2000) they describe the cellular changes taking place in the same model, with particular reference to the cellular handling of calcium. They demonstrated that in isolated myocytes from the aforementioned CAVB model, cell shortening, calcium release from the sarcoplasmic reticulum (SR) and SR Ca2+ content were enhanced at low stimulation frequencies. This is an adaptive response to bradycardia to maintain the cardiac output by increasing the stroke volume. The frequency response of the calcium currents in these hypertrophied hearts produces a greater influx of calcium from outside the cell and a greater release of Ca2+ from the SR at low heart rates. This means a greater net outward current (i.e. maintenance of a relatively positive membrane potential) during the plateau of the action potential and therefore prolongation of repolarisation. These findings would appear to be consistent with the findings of our study, in that we have demonstrated a change in the repolarisation characteristic in inherited cardiac hypertrophy which results in prolongation of repolarisation which is more marked at low heart rates, with little difference at higher rates. These findings corroborate our observation of an increased separation of the QT/RR curves at slower heart rates, and may implicate abnormal calcium handling as the causative factor for the repolarisation abnormalities.

These changes in cellular electrophysiology appear to be indicated in the genesis of triggered activity mediated arrhythmias due to the potentiation of early after-depolarisations (EADs) and delayed after-depolarisations (DADs) in this model (Vos et al. 1998), and are known to be important in clinical cases of congenital or acquired long QT syndromes. It is possible therefore that the ability to assess the rate responsiveness of QT using this method may provide useful prognostic information in patients with hypertrophic cardiomyopathy.

6.8.2 Increased Variation in The QT-RR Relationship

The finding in our study of an increased mean 24h SD of J indicates that the range of values of J (which dictate the gradient and shape of the exponential curves) is increased relative to controls. This in some ways may be indicative of the same phenomenon described by Atiga et al who elegantly demonstrated mutation specific changes in the QT-Variability Index (QTVI) (Atiga et al. 2000). In their study, the degree of variation of QT relative to variations in heart rate was far greater in patients with HCM mutations considered to be associated with a higher risk of SCD. On top of this, the coherence between changes in QT and RR was much lower in this same group. In our study, the patients were similar on symptomatic criteria but we had no genotypic data to enable us to create subgroups.

6.8.3 Limitations

HCM is defined on the morphological criterion of magnitude of LVH. However, a genetic perspective identifies several hundred, or more, diseases of the cardiac

sarcomere. In this context, it is important to determine whether the repolarisation differences demonstrated in papers such as that of Atiga (Atiga et al. 2000) are related to SCD irrespective of the mutation present. In other words, are repolarisation abnormalities predictors of adverse outcome independent of genetic cause. In this study, the genetic mutations were unknown and the rates of SCD and positive electrophysiological study were zero. Some of these issues will be dealt with in the next chapter.

Although the group sizes in this study were of reasonable size, a significant percentage of patients with HCM were excluded from the analysis due to the quality of the recordings. Sixty-five percent of unsuitable recordings were excluded because of noisy recordings that interfere with the automated measurement of T_{end}. This may be improved by a better 'hook-up' of electrodes to the patient as many of the patients put the electrodes on themselves, having been supplied with a pack and instructions. In addition, there was no ECG monitoring of the T wave morphology or quality of the signal at the time of hook-up. This was in part due to the fact that the recordings were taken for assessment of arrhythmias and QT analysis was performed as an 'add-on' study.

The remaining 35% of subjects were excluded because of the inability of the analyser to determine the end of the T wave. This can occur with this method if the T waves are of complex morphology with a biphasic component. The combination of a prolonged QT interval along with a biphasic wave causes the analyser to open the T

gate early relative to the end of the T wave. If the ST segment is down-sloping, followed by a positive T wave, the apex of T will be determined as the junction between the ST and the upward limb of the T wave as this is a zero slope point (see chapters 3 and 4 for further explanation). The T_{end} will subsequently be defined by the automated algorithm as the point at which the slope of the T wave (on the upward limb) crosses a threshold and will therefore measure T_{apex} rather than T_{end}. The fact that several subjects with such complex T waves have been excluded may have introduced bias into the study as one might expect these findings to be associated with more marked abnormalities of repolarisation. At present, an additional hardware component is currently under development which will enable the user to define a 'region of interest' window that should enable the blinding of the analyser to all segments of the T wave apart from the intended segment, namely T_{apex} to T_{end}. For further reassurance, the included and excluded patients will be compared in more in the next chapter

6.9 Conclusions

This study provides evidence that in patients with hypertrophic cardiomyopathy there are marked abnormalities of repolarisation, including prolongation of repolarisation (QT) which is more marked at low heart rates. In addition, there is an increased variation in the relationship between QT and RR. Although it is dangerous to extrapolate directly from animal studies, there do appear to be some parallels with studies that have shown similar changes which have been described as 'electrophysiological remodelling' (Tomaselli and Marban 1999) and go hand-in-

hand with the adaptive structural changes that enable the heart to contract under adverse haemodynamic or structural circumstances. These changes are likely to be implicated in triggered activity mediated arrhythmias and it would therefore seem appropriate to engage this method in a larger prospective study to assess its ability to risk stratify these patients.

In the era of implantable defibrillators, which have been shown to be effective in secondary (and to a lesser extent primary) prevention of SCD in many conditions including HCM (Maron 2000), the importance of further tools for the (preferably non-invasive) risk assessment of these patients has never been greater.

Chapter 7

Correlation between Repolarisation Dynamics and Accepted Risk Factors in hypertrophic Cardiomyopathy

7.1 Introduction

In the previous chapter we demonstrated significant abnormalities in repolarisation parameters in an unselected group of patients with HCM relative to healthy controls. Previous clinical studies designed to assess the risk of SCD in HCM have proposed several risk factors to stratify these subjects and these are summarised in table 7.1 . To be clinically useful, a test must be specific, so as not to include a large proportion of patients who will never have an event, and also sensitive, that is to say that there will be few people who slip through the net with a negative result yet go on to have an event. Due to the overall low risk of SCD in HCM, populations must be large and follow-up protracted to increase our ability to determine risk factors.

One clinical feature that has been shown to be more prominent in groups of patients with sudden death is the presence of severe left ventricular hypertrophy. The reasons for this are not immediately apparent. However, if one considers that a greater wall thickness causes a greater loss of ventricular compliance, a subject may experience more symptoms attributable to diastolic dysfunction with impaired filling of a stiff ventricle. This could lead to greater haemodynamic intolerance of tachyarrhythmias, whether supra-ventricular or ventricular in origin. Another possibility is that the increased myocardial oxygen demand of the excessively hypertrophied ventricle results in ischaemia and subsequent arrhythmias or further diastolic and/or systolic impairment. A third potential explanation could be that the electrophysiological remodelling associated with myocyte hypertrophy (Tomaselli and Marban 1999,

Holter recordings were analysed for arrhythmias and all episodes of supraventricular tachycardia (SVT), non-sustained ventricular tachycardia (NSVT), or VT were logged. Holter recordings were also analysed for repolarisation behaviour, as described in previous chapters. Exclusion criteria were as documented in chapter six, and in total, 32 patients' recordings were analysed in the best available channel for QT dynamics.

7.4 Results

Statistical Differences between Included and Excluded Patients:

To reduce the possibility of a false positive result due to the exclusion of 50% of patients' recordings, we compared the MRI data of the patients whose recordings were excluded with those included by unpaired t-tests. There was a slightly higher ejection fraction in the excluded group (75% vs 70%, $p<0.01$) but all other measurements were comparable, with no statistically significant differences (Table 7.1). This suggests that the patients who were excluded had overall similar characteristics with a similar degree of severity of disease. It can be seen that there was a considerable range in the degree of hypertrophy and LV mass. In addition, there was no difference in the incidence of arrhythmias between the included and excluded groups (Table 7.3).

Table 7.2: Clinical and MRI characteristics of HCM patients whose Holter recordings were included in the analysis compared with those excluded. Data are expressed as mean 24h values ± SD (range)

	Included (n=31)	Excluded (n=29)	P value
Age	38 ± 9 (46)	40 ± 11 (33)	0.73
BSA (kg/m^2)	2.02 ± 0.22	1.920±0.15	0.06
SV (ml)	88±30 (139)	75±19 (84)	0.03
EDV (ml)	115±37 (166)	107±27 (104)	0.15
LV mass (g)	230±101 (413)	204±75 (286)	0.12
LV mass index (g/m^2)	112±41 (151)	106±39 (171)	0.28
Max end systolic thickness (mm	32.1±6.7 (23)	32.4±5.9 (25)	0.42
Max end diastolic thickness (mm)	26.1±5.8 (22)	26.5±4.6 (20)	0.38

Relationship between Arrhythmias and QT Analyses:

Results of the Holter arrhythmia analyses are laid out in table 7.3. On Holter analysis, the presence of non-sustained VT and SVT (>3 beats) was commonplace and present in almost 30% of subjects. None had atrial fibrillation. As the presence of NSVT and LV wall thickness have both been proposed as independent risk factors for SCD, we compared the patients with and without NSVT, in terms of both the MRI data and the QT data(Figs 7.1 A-C). There was no significant difference between the groups in either MRI measurements or QT analysis. Mean values and significance levels are set

out in table 7.4. Equally there were no differences seen in any of the MRI measurements in those patients with NSVT and those without.

Table 7.3 Results of Holter Arrhythmia Analysis:

Arrhythmia	Included Number/Total	Excluded Number/Total
AF	0/ 31 (0%)	0/29 (0%)
SVT (>3 beats)	8/ 31 (26%)	9/29 (31%)
Non-sustained VT (>3 beats)	9/ 31 (29%)	8/29 (28%)

Table 7.4 MRI and QT Characteristics in Patients with and without NSVT

	No NSVT mean (SD)	NSVT mean (SD)	Significance
QTo (ms)	454 (24.5)	459 (33)	p = 0.6
J	0.41 (0.08)	0.41 (0.09)	p =0.97
24h SD of J	0.16 (0.43)	0.19 (0.23)	p = 0.88
Ejection fraction (%)	72 (7)	74 (6.3)	p = 0.33
Stroke Volume	77 (21)	90 (32)	p = 0.07
End diastolic volume (ml)	107 (27)	121 (38)	p = 0.11
End systolic volume (ml)	29.6 (11)	30.7 (11)	p = 0.71
Average mass (g)	219 (83)	215 (100)	p = 0.87
End systolic maximum thickness (mm)	32.1 (5.8)	32.5 (7.0)	p = 0.81
End diastolic maximum thickness (mm)	26.0 (5.0)	26.7 (5.5)	p = 0.62
LV Mass index (g/m^2)	111.6 (36.7)	104.1 (39.0)	p = 0.50

Relationship between QT Analyses and MRI Data:

Having established that the presence of NSVT on Holter in this group is relatively commonplace, and that there do not appear to be differences in other parameters in those with NSVT, we compared the MRI data with the results of the 24h QT-RR analysis. There was a strong and statistically significant relationship between the mean 24h value of QTo and the MRI assessment of LV average mass ($r = 0.52$, $p < 0.005$) and LV mass index ($r = 0.49$, $p < 0.01$). A relationship was also present, although less strong, for maximum end systolic thickness ($r = 0.39$, $p < 0.05$). Statistical significance was not reached for end diastolic maximum thickness ($r = 0.2$, $p = 0.27$). The correlation plots are shown in figures 7.2 (A – C).

No significant relationship was demonstrated between the exponent J and the MRI data. In light of a recent post-mortem study (Varnava et al. 2000) which demonstrated a significant inverse relationship between heart mass and age of death, we compared the MRI data with age and found no correlation.

Figure 7.1 A

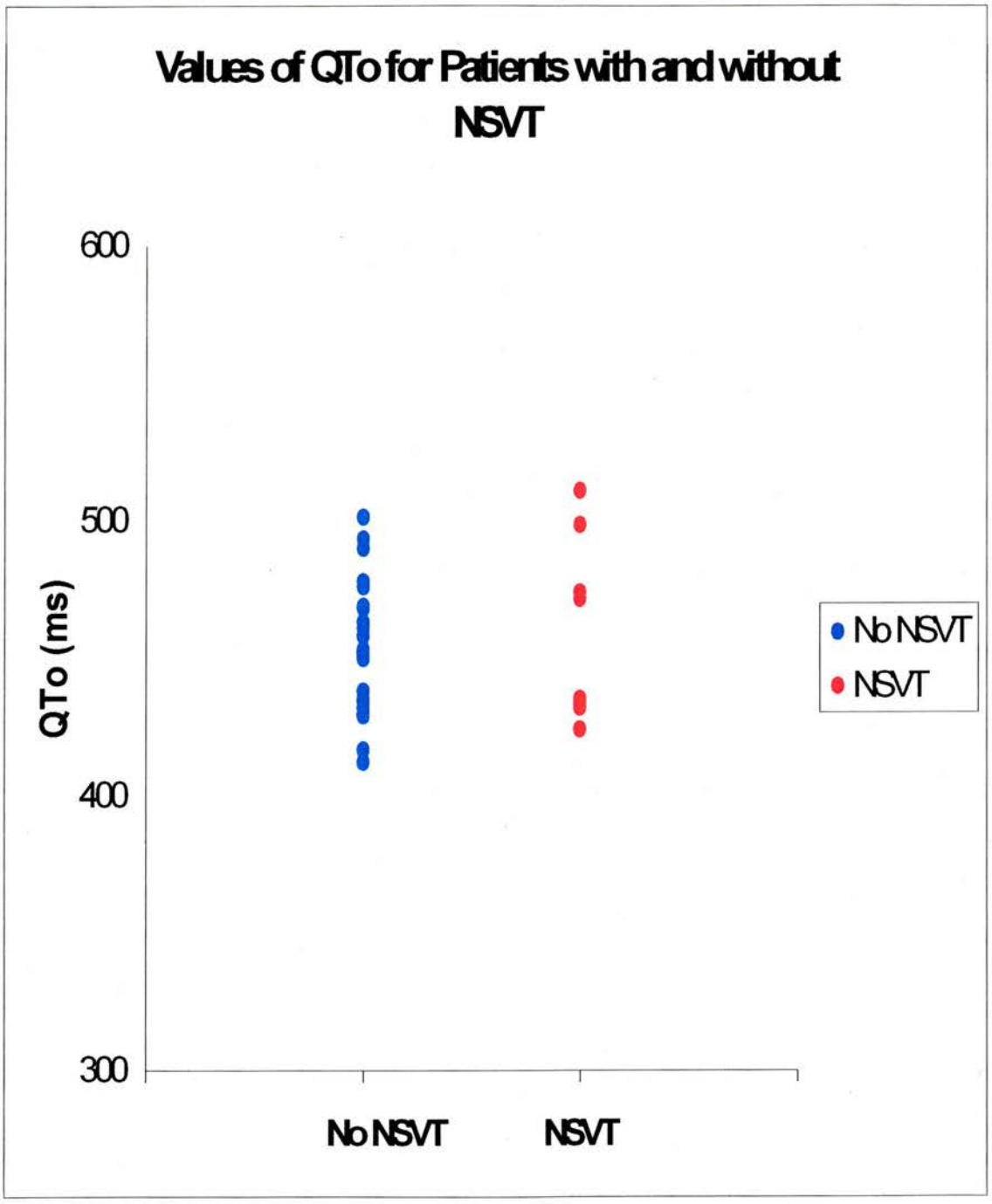

Values of QTo for Patients with and without NSVT
600
500
400
300
QTo (ms)
No NSVT
NSVT
No NSVT
NSVT

Figure 7.1 B

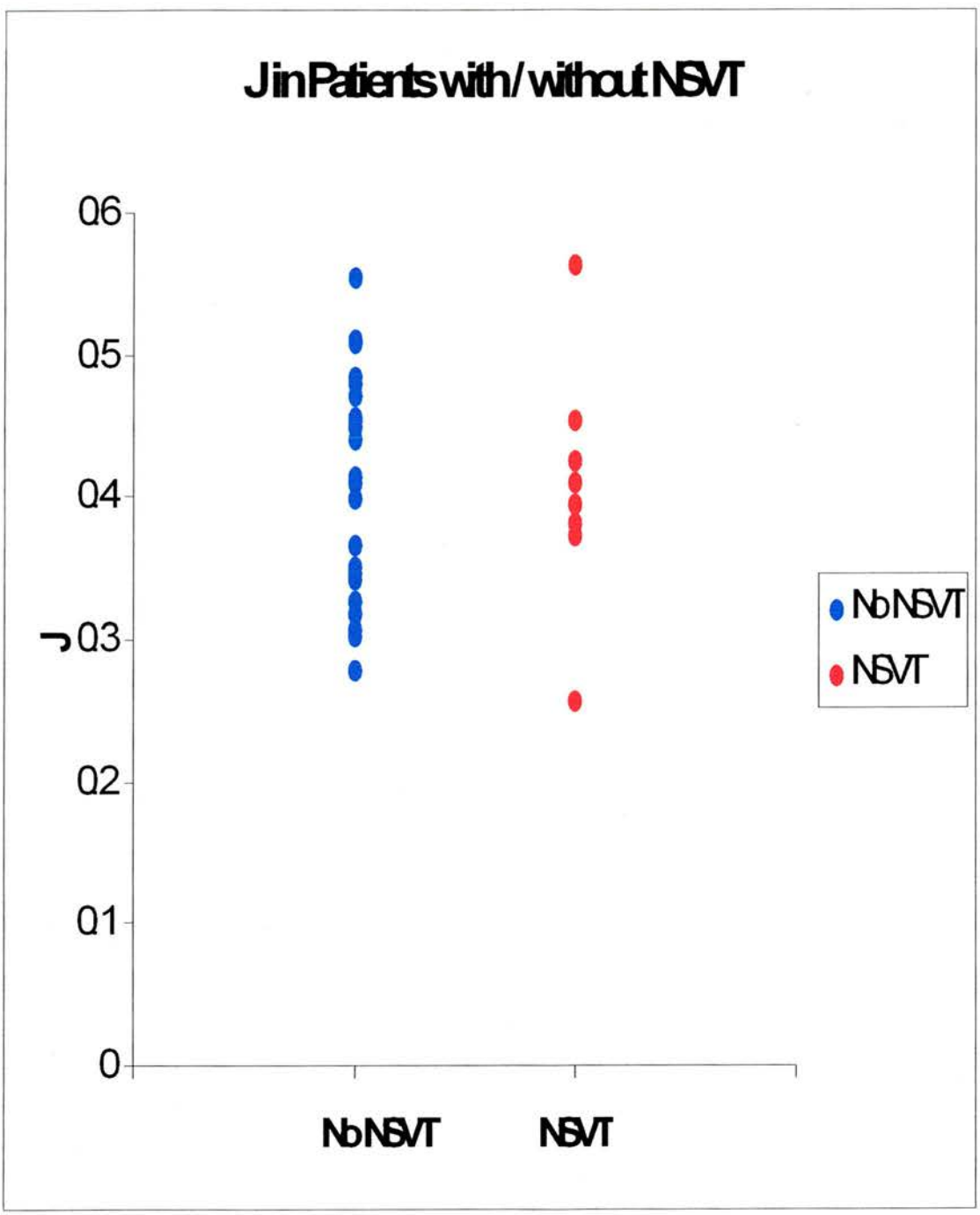
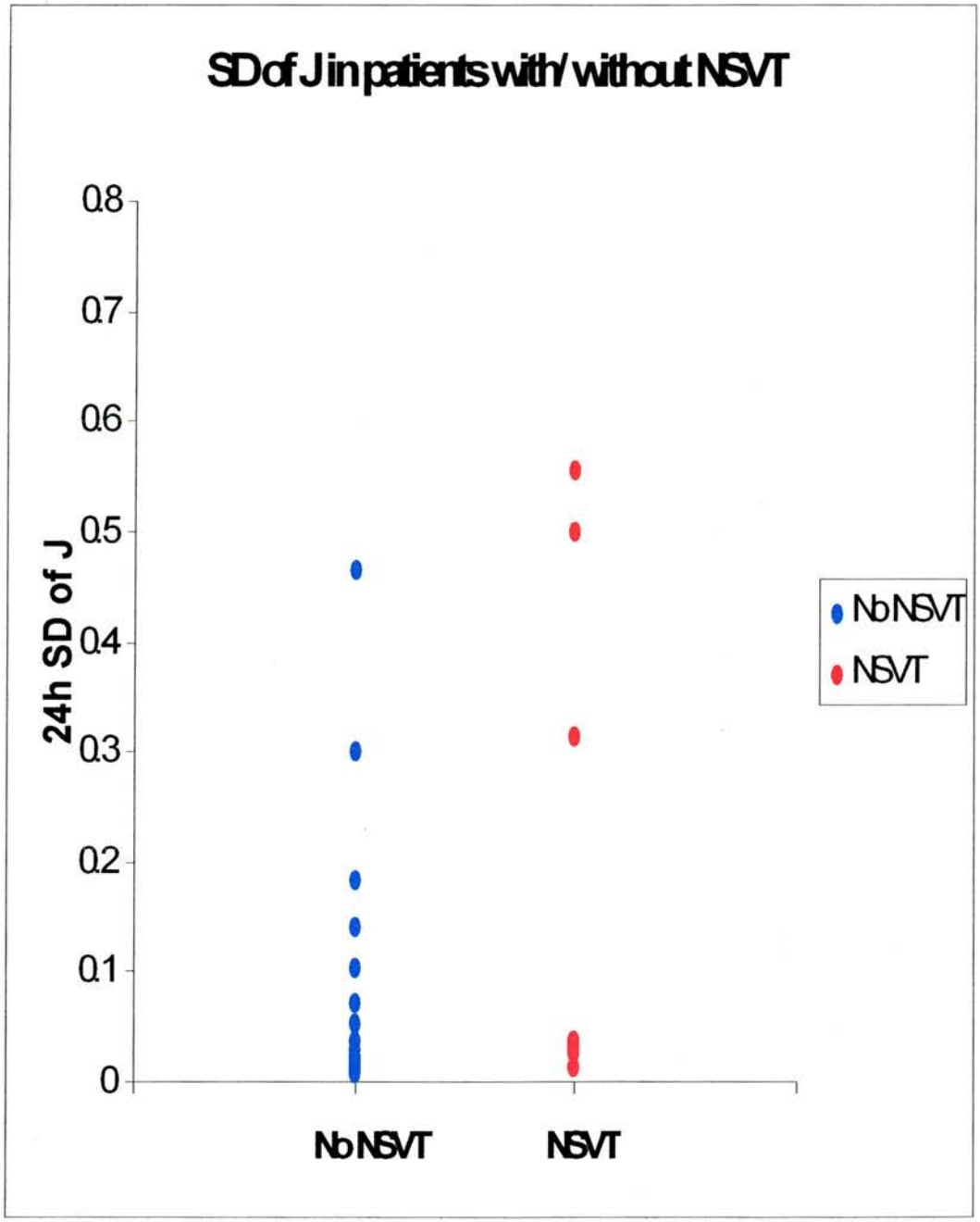

J in Patients with / without NSVT
0.6
0.5
0.4
0.3
0.2
0.1
0
J
NbNSVT
NSVT
NbNSVT
NSVT

Figure 7.1 C


SD of J in patients with/ without NSVT
24h SD of J
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
NbNSVT
NSVT
NbNSVT
NSVT

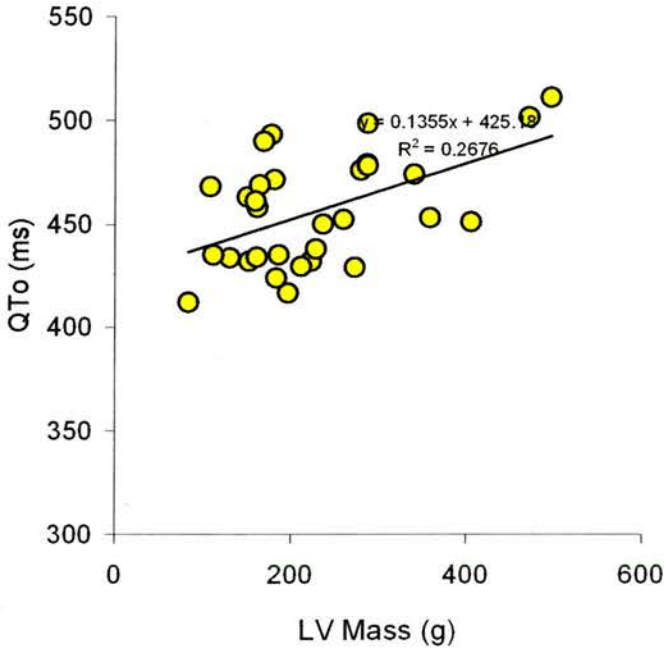


Figure 7.2 A:

QTo versus LV average mass

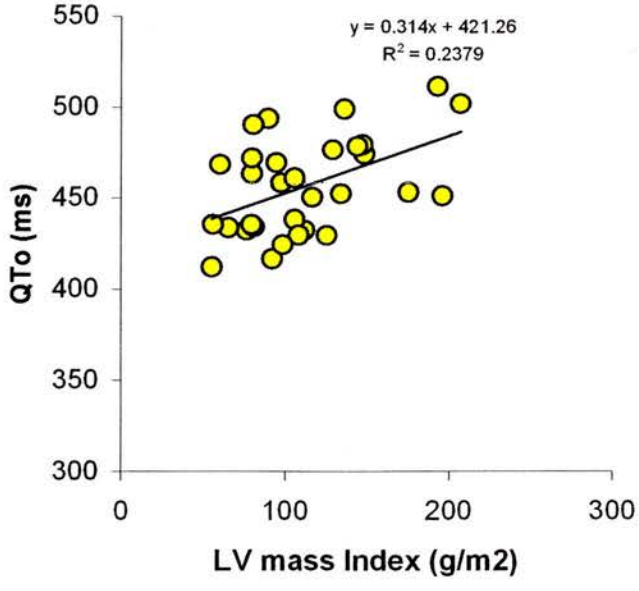


Figure 7.2 B:

QTo vs LV Mass corrected for Body Surface Area (LV mass index)

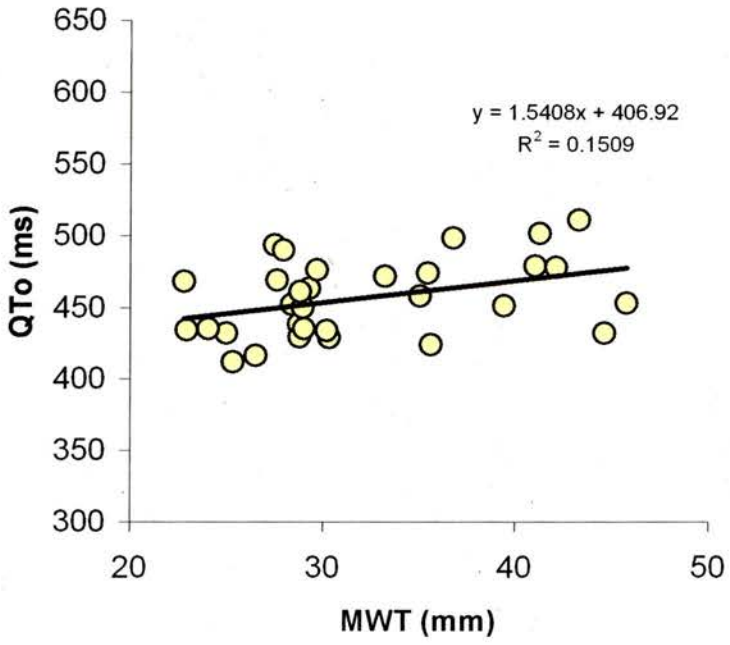


Figure 7.2 C: QTo vs Maximum (systolic) wall thickness

7.5 Discussion

7.5.1 Comparison of subjects with and without Non-sustained ventricular tachycardia on Holter monitoring.

No difference was observed between any of the 24h QT-RR when patients were divided according to the presence of NSVT on 24 or 48h Holter monitoring. This is in keeping with the previous studies of risk factors in HCM which have shown that the presence of NSVT is seen in up to 50% (Fananapazir et al. 1992). In Fananapazir's article, they demonstrated that it was present in only 41% of patients who had a cardiac arrest. Of 115 patients with NSVT on Holter, 10% had a cardiac event compared with 5 of 155 patients without VT on Holter (4%). Only when patients had experienced episodes of pre-syncope did the presence of NSVT carry any prognostic

information. In our small study, it is not surprising that there is no apparent difference between the two groups in light of the existing evidence on the frequency of occurrence of NSVT in these subjects.

7.5.2 Comparison of QT data with MRI Findings

Magnetic resonance imaging was employed to assess left-ventricular dimensions and mass in this study as it has been shown to be more accurate and reproducible than methods employing two-dimensional echocardiography in several patient groups including dilated and hypertrophic cardiomyopathy, hypertension and athletic hearts (Bellenger et al. 2000, Allison et al. 1993, Bottini et al. 1995, Pons-Llado et al. 1997, Pluim et al. 1997, Chuang et al. 2000). There is the additional advantage that high quality images can be obtained in many more patients than could be expected with echo (Bellenger et al. 2000b).

Calculating each individual's mean 24h 'rate corrected' QT (QTo) by continuous assessment of the QT/RR relationship using Neilson's variable exponential model has allowed us to compare cardiac repolarisation characteristics independently of heart rate with measurements of hypertrophy.

A strong correlation is seen between QTo and both LV average mass and LV mass index. This suggests that the 'electrophysiological remodelling' seen in hypertrophic heart disease is a progressive phenomenon that occurs either in response to, or as a direct compensatory mechanism of impaired sarcomeric function. Spirito and Maron

have published two large scale studies on the association between hypertrophy and sudden cardiac death. In the earlier of the two (Spirito and Maron 1990) which was a retrospective study, they demonstrated that the HCM patient group which had died suddenly was more likely to exhibit marked left ventricular hypertrophy than the control group of HCM patients who had not. Maximal LV wall thickness was greater (26±7mm vs 21±5mm). A more discriminating measurement however was the left ventricular wall thickness index (LVWTI). This was calculated by dividing the ventricle into four segments and adding the wall thicknesses together to reflect the degree of overall hypertrophy. The SCD group had a higher LVWTI (76 ± 20mm) compared to the control group (62 ± 13 mm). Particularly marked and diffuse hypertrophy with a maximum wall thickness of > 30mm or > 25mm in two or more segments was eight times more common in patients with SCD. A few patients with SCD had less marked hypertrophy (4/29), although three of these were pre-adolescent children and they remark that the hypertrophy would have been more marked had they corrected the values for body weight. The patients in this study were all relatively asymptomatic (NYHA I to II), similar to our own group.

In the more recent article, Spirito et al published the results of a long-term follow-up study of patients with HCM (Spirito et al. 2000). Of 480 patients followed over a mean of 6.5 years, 65 patients died (14%), 23 suddenly, 15 of heart failure and 27 of non-cardiac disease or stroke. The risk of SCD increased progressively and in direct relation to wall thickness. Risk ranged from 0 per 1000 person years for a LVMWT of 19mm or less, to 18.2 per 1000 patient years for wall thicknesses of 30mm or

more. Left ventricular wall thickness index (see previous paper) was not measured in these subjects. The recent article by Varnava et al (Varnava et al. 2000) which examined hearts of patients with HCM who had died, they found a significant negative inverse relationship between age and heart weight, implying that patients are likely to die younger if gross hypertrophy is present.

7.6 Conclusions

The measurement of 24h repolarisation dynamics, with extrapolation of the QT/RR curves to give mean 24h values of QTo has provided valuable information regarding the nature of the electrophysiological remodelling in HCM. The QT (and by inference the action potential) prolongation in HCM appears to progress with the degree of hypertrophy. The findings in our study support a potential causative role of abnormal repolarisation in the sudden death due to massive hypertrophy. From the MRI data a closer correlation was found between left ventricular average mass and LV mass index than the maximum left-ventricular wall thickness. It may be that the MRI assessment of LV mass or LVMI may provide more useful information for risk stratification than echocardiographic parameters. A prospective study to assess the value of 24h dynamic QT-RR and MRI assessment of patients is necessary to evaluate the potential of these non-invasive investigations in risk stratifying subjects with HCM.

Chapter 8

24h Repolarisation Characteristics in Cardiac Arrest Survivors: The Influence of β-Blockade

8.1 Introduction

Sympathetic activity is known to be arrhythmogenic in many clinical and experimental situations. Indications for the use of β-blockers have broadened in recent years due to the increasing evidence supporting their use in the management of patients with heart failure. Several large studies have shown a marked reduction in all cause mortality, sudden cardiac death, worsening of heart failure and hospital admissions (Merit-HF, CIBIS II, COPERNICUS). One of the most striking reductions in mortality is in the subgroup of sudden cardiac death. In all of the major trials of beta-blockade in heart failure there is a 40-50% reduction in the incidence in sudden death. This appears to be largely due to a reduction in arrhythmic death. There is also evidence that β-blockers reduce the incidence of sudden death in patients following myocardial infarction (Olsson and Wikstrand and Warnold 1992) and hypertensive patients.

The mechanisms for catecholamine induced cardiac arrest are numerous, including ischemia and infarction, macro-reentrant arrhythmias and ventricular fibrillation. Given that the likelihood of triggered activity is increased in patients with prolongation of the QT interval, and having demonstrated that patients with hypertrophic cardiomyopathy and heart failure have prolongation of QTo and J (chapters 4,5,6), we evaluated 24h Holter recordings from a group of patients who had survived out of hospital cardiac arrest (OHCA) and had received implantable

cardioverter defibrillators (ICDs) for secondary prevention. We compared patients who were taking β-blockers with those who were in order to assess whether differences existed in the QT/RR relationship.

8. 2 Hypotheses

In chapter four we examined the repolarisation characteristics of a group of patients with heart failure who were subsequently divided into NYHA classes. We demonstrated a progressive prolongation in QTo and an increase in J with worsening functional class. We hypothesised that the increase in J may have been due to an increase in the sympathetic tone. In this study we set out from that hypothesis to study this heterogeneous group of patients who have varying degrees of heart failure and reduced ejection fractions. The goal was to determine whether those subjects on beta-blocker therapy have increased values of QTo (as one would expect as sympathetic stimulation shortens APD and QT), but also a reduction in J which should be a rate-independent marker of the rate dependence of QT, in contrast to slope.

8.3 Subjects and Methods

123 patients who were under follow up for their ICD at the Royal Infirmary of Edinburgh (n=20) or Glasgow Royal Infirmary (n=103) were enrolled into the study. Note was taken of their diagnosis, past medical history, ejection fraction as determined by angiography, echocardiography or radio-nucleide methods, medication at the time of enrolment and an assessment of their functional (NYHA) class was

made. Baseline resting ECG recordings were taken on all patients. All patients had been stable on therapy for at least one month. All patients had ambulatory 24h ECG recordings made at the time of enrolment. Exclusion criteria were: 1) Bundle branch block or QRS duration > 0.14s; 2) Background bradycardia pacing; 3) Atrial fibrillation or frequent (>5%) ectopic beats; 4) Regular medication of amiodarone or sotalol.

A total of eighty-three 24h ECG recordings were made, of which forty-one were of sufficient quality for QT and RR interval analysis. 24h QT/RR parameters for individuals which were then averaged for the two groups. The groups were compared using student's unpaired t-test.

8.4 Results

8.4.1 Baseline characteristics

Baseline characteristics of the two groups are given in table 8.1. The significance continuous data was assessed by t-test, and categorical data by χ^2 testing.

Patients were well matched for age, sex, ejection fraction and NYHA class. Although the two groups contained subjects with heterogeneous aetiologies for their arrhythmias, these were balanced between the two groups

Table 8.1: Baseline characteristics of ICD patients divided into two groups according to whether or not they were taking β-blockers.

	No Beta Blockers	Beta Blockers	p value
Sex (m/f/total)	20 /5 / 25	15/ 1/ 16	NS
Age	56	54	NS
Ejection fraction	31%	29%	NS
NYHA Class	1.6±0.7	1.8±0.7	NS
Previous MI	17/25 (68%)	13/16 (81%)	NS
Primary VF	3/25 (12%)	1/16 (6.3%)	NS
HCM	1/25 (4%)	1/16 (4%)	NS
ARVD	2/25 (8%)	1/16 (6.3%)	NS

Table 8.2: 24h QT-RR Characteristics. Data are mean 24h values (SD)

	RR	QT	QTo	S	J	24h SD of J
NBB	885 (102)	417 (36)	448 (31)	0.18	0.38	0.114
n = 25				(0.05)	(0.10)	(0.036)
BB	1005	452 (44)	461 (35)	0.15	0.31	0.151
n = 16	(131)			(0.06)	(0.13)	(0.088)
p	<0.01	<0.01	0.2	0.06	<0.05	0.6
value						

8.4.2 24h QT-RR Characteristics

As expected, the group taking β-blockers had a slower heart rate, as indicated by the longer mean 24h RR interval (1005ms vs 886ms, $p<0.005$) with a correspondingly longer mean 24h QT (452ms vs 417ms, $p<0.01$). When both groups are compared with the control group in chapter 5 (heart failure) it can be seen that QTo is longer and J is greater in this group compared to healthy volunteers. The abnormalities are less marked than the group of patients with heart failure, but the degree of LV impairment was more marked and the functional class worse in that group.

The average mean 24h QTo (QT at an RR interval of 1000ms) was not significantly different (461ms vs 448ms, p=NS) between the BB and NBB groups. When the mean slopes are compared between the two groups, it was significantly shallower in the BB group (0.149 vs 0.186, $p<0.05$), however this parameter is rate dependent as the QT/RR relationship is described by an exponential curve and is less steep at low heart rates. The exponent J which describes the shape and gradient of the QT/RR relationship was also reduced in the β-blocker group (0.379 vs 0.313, $p<0.05$), indicating that overall, the curve in the group taking these agents was indeed less steep (see figure 8.1) throughout the physiological range of heart rates. The variation in the QT/RR relationship (indicated by the mean 24h SD of J) was slightly greater in the group on β-blockers (p=NS).

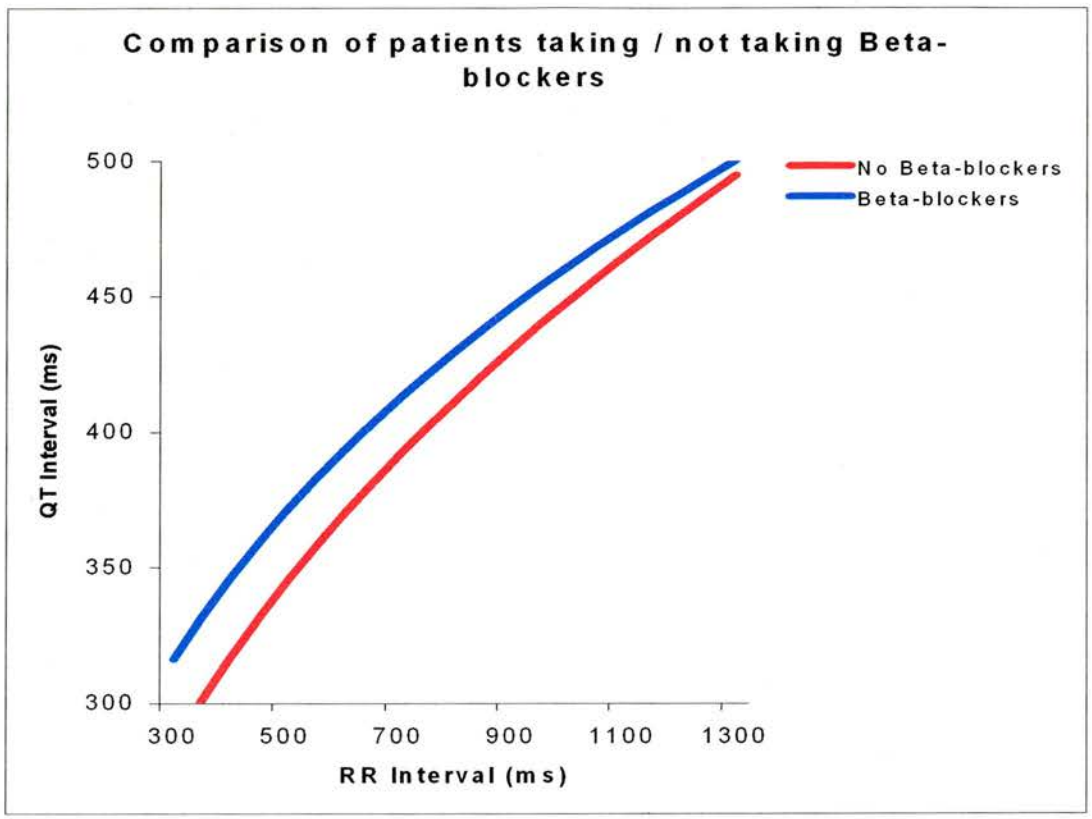


Figure 8.1

Constructed QT/RR curves from grouped population values of mean 24h QTo and J. It can be seen that the patients on β-blockers tend to have a flatter curve with less shortening of QT at higher heart rates and overall tend to have a slightly longer QT interval.

8.5 Discussion

The influence of the sympathetic nervous system on cardiac repolarisation has been studied in the past using several different approaches. Due to the blunting effects of beta-blockade on heart rate, it is often difficult to make comparisons. In pacing studies it has been possible to show that incremental atrial or ventricular pacing produces less shortening of the QT interval than exercising to similar rates. Also, β-blockade reduces the exercise induced shortening of the QT interval for any given heart rate (Fananapazir and Bennett and Faragher 1983). In patients with autonomic neuropathy or denervated (transplanted) hearts, there is less diurnal variation in QTc than one sees in health (Bexton and Vallin and Camm 1986). However, these studies used linear models of the QT-RR relationship and were performed in patients who by and large had normal left ventricular function.

This study, although not a prospective study, appears to indicate that the rate dependence of the QT interval is indeed reduced in the group of patients on β-blockers. The two groups were well matched for age, sex, left-ventricular function and functional class and these factors which have been shown to influence the QT interval are therefore unlikely to have skewed the results.

The mechanisms through which the sympathetic nervous system can precipitate arrhythmias have been extensively studied (Malliani and Schwartz and Zanchetti 1980) and beta blockers have been shown to prevent this (Schwartz et al. 1985). In patients with the congenital long QT syndrome, left cervical stellectomy was an

accepted treatment (Schwartz et al. 1991). This surgical treatment has been shown to increase the ventricular fibrillation threshold in animals susceptible to arrhythmias (Schwartz and Stone and Brown 1976, Schwartz and Stone 1980). More recently, the use of β-blockers in association with the implantable defibrillator has become more accepted.

The role of β-blockers in prevention of SCD in man has been established in the post-myocardial infarction population for many years (Chadda et al. 1986). More recently, a beneficial effect in terms of mortality due to worsening of heart failure or SCD has also been shown in patients with ischaemic or idiopathic cardiomyopathy (CIBIS-II Investigators and Committees 1997, Merit-HF Study Group 1999). Much of this reduction in mortality is due to a reduction in SCD, a feature that has not been shown to exist with established agents such angiotensin converting enzyme inhibitors (ACEI) or angiotensin II antagonists (AIIA) (Garg and Yusuf 1995,The SOLVD Investigators 1991, ELITE II).

One of the interesting observations in our study is that β-blockers tended to produce a rate-independent lengthening of QT (although not statistically significant), but what was more marked was the reduction in the rate dependence, indicated by the lower slope of the curve throughout most of the physiological range, reflected by the lower value of J (see figure 8.1). It may be that this reduced rate dependence may be prolonging the refractoriness of the ventricle at higher heart rates, making it more difficult for re-entrant circuits to be activated and maintained (reduced excitable gap).

Secondly, increased sympathetic activity has been shown to increase the propensity to delayed after-depolarisations and triggered arrhythmias. Thirdly, heart rate will not accelerate with sympathetic activation, reducing the ischaemic burden which can create regional variations in refractoriness.

If repolarisation is important in arrhythmogenesis in heart failure and other conditions (Tomaselli et al. 1994), we must conclude from these results that it is not purely a lengthening of QT that is critical, as this occurs in healthy subjects when sleeping (Browne et al. 1983). In previous chapters we questioned the relevance of quoting a value of corrected QT at an arbitrarily chosen reference heart rate if the overall characteristic of the QT-RR relationship differs between the two groups. This study would appear to underline those comments as here we see a normal or slightly increased QT at an RR interval of one second in the group likely to be more protected against arrhythmias, but a flatter response to changes in RR when patients are on β-blockers. This raises the question of whether the slope or shape of the QT/RR curve is more important in the risk of arrhythmias due to abnormal repolarisation.

8.6 Limitations

The patients in this study had varying aetiologies for ventricular arrhythmias. The majority of patients had a history of previous myocardial infarction and resuscitated out-of-hospital cardiac arrest. The arrhythmia responsible for the index events varied from ventricular to polymorphic VT and VF. The substrate for these arrhythmias differs, with VT usually being due to a macro re-entrant circuit involving the border-

zone of an old infarct site. To initiate and maintain VT in this situation requires two conditions: a suitably timed ectopic beat and; secondly unidirectional block or slowed conduction in one of the limbs of the circuit. Ventricular fibrillation is often a result of degeneration of the re-entrant circuit but can arise directly from the ectopic beat in unstable situations. It is not clear whether the influence of repolarisation in both these situations is likely to produce the same results. While one might expect prolongation of repolarisation to generate more ectopy due to early or delayed after-depolarisations, a prolongation of the refractory period can in certain situations be anti-arrhythmic, and this forms the basis for many of the anti-arrhythmic agents in use today. In cases of ventricular tachycardia, prolongation of refractoriness may produce prolonged refractoriness in one limb and render the arrhythmia non-inducible.

The patients in this group were divided according to whether they had been on chronic therapy at stable dosages for one month. While this has the advantage of increasing the likelihood of steady-state plasma levels (assuming 100% compliance), it increases the risk that the observations are chance findings and that the differences observed are due to population differences. Fortunately the groups were well matched for several factors known to influence repolarisation and this is therefore less likely, however, a prospective study with assessment of repolarisation before and after beta-blockade would have been more valuable.

The spatial dispersion of repolarisation is known to be important in increasing the likelihood of initiation and maintenance of ventricular arrhythmias and measurement of QT dispersion has shown that in many groups at risk of sudden death the spread of surface QT intervals is greater. Using 24h Holter recordings restricts our ability to comment on this.

8.7 Conclusions

Long-term treatment with β-blockers appears to result in a reduced rate dependence of QT. There are theoretical reasons why this might be advantageous for preventing arrhythmias in patients with impaired ventricles or a history of aborted sudden cardiac death. Further research is required to assess whether increases in the rate dependence of QT can be implicated in the onset of arrhythmias.

Chapter 9

Circadian Variation in the incidence of Sustained and Non-Sustained Ventricular Arrhythmias in Patients with Implantable Defibrillators

9.1 Introduction

Sudden cardiac death is generally defined as an unexpected cardiac death preceded by no apparent symptoms or by symptoms with a duration of less than one hour. In the United States 300,000 cases of SCD occur each year (Kuller 1980). Most cases of SCD are caused by ventricular fibrillation, often preceded by ventricular tachycardia (Schaffer and Cobb 1975, Pratt and Francis and Luck 1983). Eighty percent of SCD occurs in association with coronary artery disease (CAD). A healed myocardial infarction is a frequent post-mortem finding, although acute myocardial infarction is less common (Reichenbach and Moss and Meyer 1977). Most of the remaining 20% of patients have one of the cardiomyopathies although sudden death is sometimes seen in subjects with no evidence of structural heart disease.

Unfortunately, despite increased resuscitation training amongst the public and health-care professionals and the wider availability of semi-automatic defibrillators for ambulance teams (and even automatic defibrillators in public places), the mortality remains high. In recent years, internal implantable cardioverter-defibrillators (ICDs) have been shown to be effective in improving survival in high risk patients (e.g. cardiac arrest survivors) when compared to treatment with amiodarone or EP guided anti-arrhythmic therapy (Anderson et al 1997 (AVID), Connolly et al 2000 (CIDS), Wever et al 1995). In addition, ICDs have been shown to dramatically improve survival in selected post-MI patients (Buxton et al 1999 (MUSTT), Moss et al 1996) (MADIT), Moss et al 2002 (MADIT II)), albeit at substantial cost, estimated at $22,800 per life-year saved (Mushlin et al 1998)

9.1.2 Circadian Variation of SCD

There is significant circadian variation in the frequency of sudden death with a relative excess during the morning. It is frequently difficult to determine whether the cause of death is a primary arrhythmia or secondary to another event such as acute myocardial infarction, which is thought to account for a third of SCD. In 1987 results of the prospective Framingham Heart Study (Willich et al. 1987) helped to resolve this problem. They analysed data on the time of death of 264 definite sudden cardiac deaths. This showed that there was a peak prevalence of death in the morning, which started to fall by 10 am. Even when additional cases of sudden death of *possible* cardiac cause were included, this peak remained. As the investigators wished to clarify whether there was a morning excess of sudden cardiac deaths independent of the morning excess of myocardial infarctions, they compared data from a previous study (Muller et al. 1985) which described the circadian variation of myocardial infarction in a similar population. Using this data they subtracted the estimated hourly incidence of death due to myocardial infarction from their own data, with the assumption that only those subjects with primary SCD remained. Following this manipulation, a striking morning peak is seen, beginning between 7 am and 8 am, peaking at around 9am and falling back to baseline levels after around 10 am. The average hourly risk of SCD was 70% greater between 7am and 9am relative to the remaining 22 hours. There were several problems with this study - firstly one of identifying all cases of SCD in a population, and secondly of determining the exact time of occurrence of what may be an unwitnessed event with the absence of a retrospective history. The conclusion of the study was that the early morning is a

high-risk period for subjects prone to arrhythmia, even in the absence of a history of arrhythmia.

The implantable cardioverter defibrillator (ICD) is one of the most ingenious advances in medical technology of the last century. These devices, from the first implant in the early 1980s, have become small enough to implant subcutaneously, with transvenous insertion of monitoring and defibrillating leads. The latest devices are now far smaller than early pacemakers, yet have the capability to continuously monitor the rhythm in both atrium and ventricle, store local electrograms (EGMs) and appropriately deliver therapies to terminate arrhythmias in a precise and timely fashion over a lifespan of several years. One of the advantages of the more modern devices is that the stored event data allows one to determine the precise nature, timing and frequency of arrhythmias, and with the additional EGM traces, determine whether the arrhythmia was supraventricular or ventricular in origin, enabling simpler reprogramming and avoidance of inappropriate therapies. This chapter assesses the circadian variation of ventricular arrhythmias in a cohort of 123 patients with ICDs under follow-up in Scotland. The purpose is to determine whether an arrhythmia 'danger period' exists in survivors of previous SCD. If this is the case, then it would urge closer scrutiny of events and circumstances at that time of day. In the case of my research, it would have particular relevance to the assessment of repolarisation dynamics.

9.2 Hypotheses

The principal hypothesis in this chapter is that primary sustained ventricular arrhythmias exhibit circadian variation in cardiac arrest survivors with implantable defibrillator devices. In addition we compare the timing of sustained ventricular arrhythmias with non-sustained arrhythmias, to establish whether their distributions vary. To assess whether any observed circadian variation was influenced by increased sympathetic activity, we divided patients into two groups according to whether they were established on regular beta-blocker therapy.

9.3 Method

One hundred and twenty three consecutive patients (24 female) were recruited into the study between June 1999 and March 2000. This represented approximately sixty percent of the Scottish ICD population at the start of the recruitment period. The conditions responsible for the arrhythmias were various, although in the majority, coronary artery disease (CAD) was the primary diagnosis. One patient had received a device for primary prevention on the grounds of perceived high risk of sudden cardiac death due to familial hypertrophic cardiomyopathy, with several family members having died suddenly. At the time of recruitment, a record was made of past cardiac and other history, medication, LV ejection fraction (by radio-nucleide, echocardiographic or angiographic methods), standard 12 lead ECG and estimation of NYHA class. Every patient was seen for routine device interrogation at quarterly intervals. The mean follow up was 12 +/- 2 months. Patients were divided into two groups according to whether or not they were taking beta-blockers (BB). Episodes of

non-sustained ventricular tachycardia (NSVT) and sustained ventricular tachycardia or ventricular fibrillation (VT/VF) recorded by the devices were documented. Supra-ventricular arrhythmias such as atrial fibrillation, sinus tachycardia or re-entrant SVTs were excluded where possible using the stored information and previously obtained patient data regarding the nature of their clinical arrhythmia. Where the timing of events was available, this was documented. Events were classified as NSVT or VT/VF by the defibrillators' internal algorithms. Episodes logged by the devices were considered discrete when separated by more than ten minutes. The significance of variation in the hourly distribution of arrhythmias was assessed by Chi-squared test.

9.4 Results

Patients were followed up for a mean period of 12 months (+/-2 months). Overall, during this period, 43 (35%) patients had ventricular arrhythmias requiring therapy from the ICD, and non-sustained VT (NSVT) was recorded in 56 patients (46%). 43 patients were taking regular beta-blocker therapy. None of the episodes occurred in the context of a history consistent with myocardial infarction. Fourteen patients (11.4%) received therapy inappropriately (usually in the form of DC shocks). These inappropriate therapies were principally due to the misinterpretation of sinus rhythm in younger patients, or due to atrial fibrillation with a rapid ventricular response rate. There was considerable overlap between the groups, as demonstrated in the Venn diagram (figure 9.1). The breakdown of the diagnostic groups, and incidence of arrhythmias is laid out in table 9.1 below. 43 patients were taking regular beta-

blockers. In this group, 51% of patients had episodes of non-sustained VT, and 33% had episodes of VT/VF compared to 34% and 37% in the group not taking beta-blockers.

Impact of Beta-blockade on the Circadian Variation of Arrhythmias

Timing data was available for 151 episodes of VT/VF and 1402 episodes of NSVT. Timing of arrhythmias was broken down into hourly intervals, and the significance of circadian variation was calculated using Chi-squared testing. For both NSVT and VT/VF, there was no significant circadian variation in those patients on BB ($p=0.72$, 0.74 respectively). In those not on BB, there was again no significant variation in the hourly incidence of NSVT ($p=0.42$). However, there was a large peak in the incidence of VT/VF between 0900h and 1000h, and the circadian variation was highly significant ($p<0.0001$). These data are represented graphically in figures 9.2 and 9.3.).

Figure 9.1: Venn diagram illustrating the number of patients experiencing arrhythmias during follow-up. The overlap between groups is most marked for those subjects exhibiting both NSVT and VT/VF.

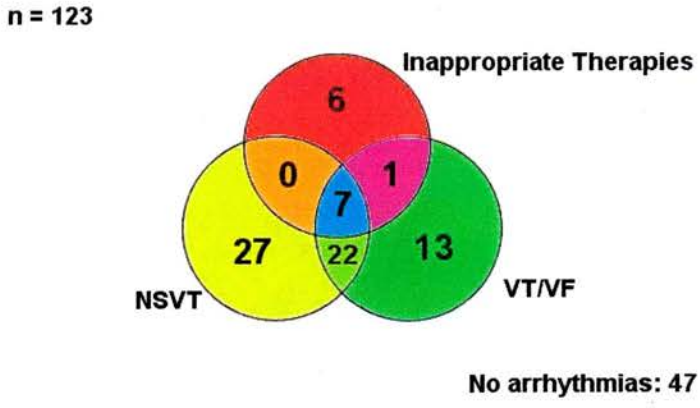


Table 9.1 Breakdown of patient characteristics according to primary diagnosis. The group with ischaemic heart disease contains those with previous myocardial infarction, with or without subsequent LV impairment, and also those subjects with CAD felt to be inoperable with a probable ischaemic component to the arrhythmias.

Diagnosis	No Beta-blockers n =80	Beta-blockers n=43
Dilated Cardiomyopathy	7 (9%)	5 (11%)
HCM	2 (2.6%)	3 (6.4%)
Arrhythmogenic RV Dysplasia (ARVD)	2 (4.3%)	2 (2.6%)
Long QT Syndrome	2 (4.3%)	1 (1.3%)
Idiopathic VT/VF	2 (4.3%)	11 (14%)
Ischaemic heart disease	52 (68%)	34 (72%)
No. of patients with VT/VF	27 (34%)	16 (37%)
No of patients with NSVT	41 (51%)	15 (34%)

Figure 9.2

Graphical representation of the absolute number of episodes of NSVT by hour of the day. The patients have been divided into two groups according to whether or not they were taking beta-blockers. Data for both groups combined is also shown.

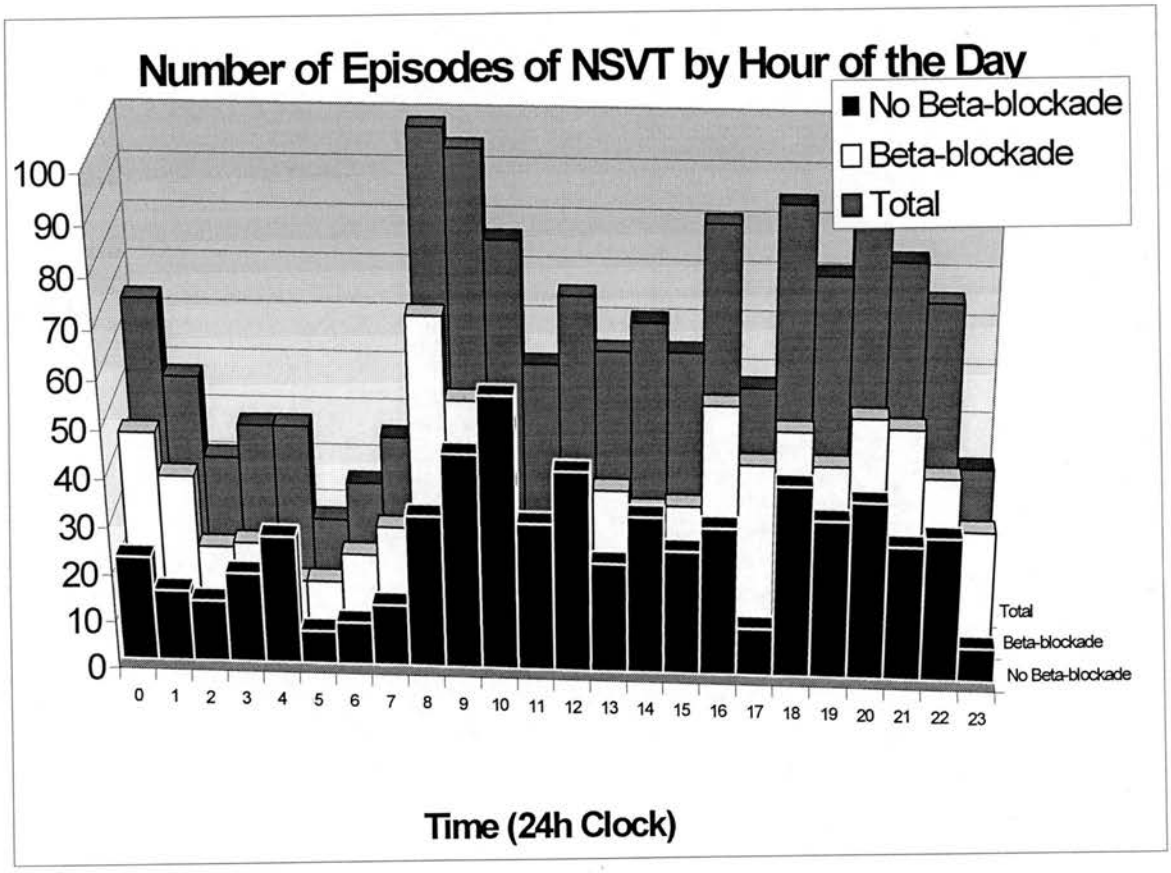
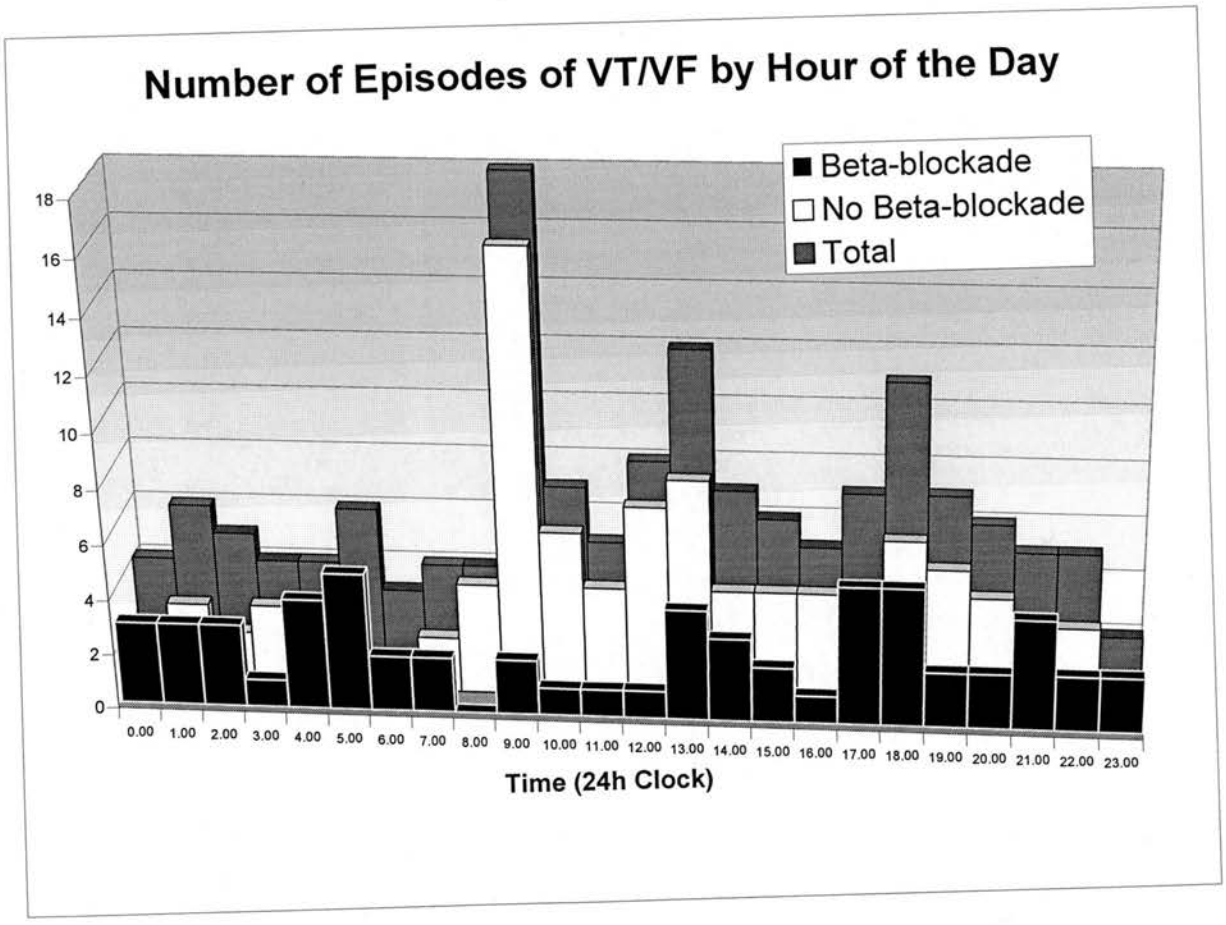


Figure 9.3

Graphical representation of the absolute number of episodes of VT/VF by hour of the day. The patients have been divided into two groups according to whether or not they were taking beta-blockers. Data for both groups combined is also shown.



9.5 Discussion

In studying this population of patients with ICDs, and by making use of the event recording capabilities of these devices, it has been possible to demonstrate a significant circadian variation in the incidence of sustained ventricular arrhythmias, relative to both expected values, and non-sustained arrhythmias. However, no significant variation was seen in the incidence of non-sustained arrhythmias relative to the expected values. This confirms the findings of the Framingham paper and others which have shown that there is a morning excess of cardiac arrests and SCD. It has the advantage however that the effective treatment of the arrhythmias by either anti-tachycardia pacing or internal DC cardioversion, and the subsequent interrogation of the EGM data and patient history, we have effectively removed the confounding factor of events caused by myocardial infarction which account for a third of cases of SCD in most studies. One limitation however is that ICDs do not generally store all EGM recordings of NSVT, and it is possible that some episodes of supraventricular arrhythmias may have been counted as ventricular. However, many devices have algorithms that assist differentiation of ventricular and supraventricular arrhythmias, and with dual chamber devices, this is clearly less of a problem. It is therefore difficult to be absolutely certain that all logged non-sustained events were truly ventricular in origin.

By examining the hourly incidence of arrhythmias in patients according to whether they are beta-blocked, we have been able to show that the morning excess of malignant arrhythmias is not present when sympathetic activity is blocked. This

strongly implicates increased adrenergic activity as a factor facilitating if not being primarily responsible for the increased incidence of morning arrhythmias. It is perhaps not surprising that a significant difference exists between the distribution of sustained VT/VF and NSVT, the former showing a large morning peak, whereas NSVT was more evenly distributed throughout the 24h period (although there do appear to be more non-sustained arrhythmias during the day with respect to night-time). This suggests that short bursts of tachycardia are commonly seen, but that in the morning, additional factors conspire to facilitate the maintenance of arrhythmias. During sleep there is a relatively higher level of parasympathetic tone, with reduced sympathetic activity. It is well known that vagal activity increases the threshold for ventricular fibrillation and is generally considered to be cardioprotective. On rising in the morning, the balance swings toward increased sympathetic activity and withdrawal of vagal tone. Levels of circulating factors including catecholamines and corticosteroids also increase. Previous studies in patients with ischaemic heart disease and heart failure have shown that reduced heart rate variability, a surrogate marker of increased sympathetic and reduced parasympathetic activity, is a risk factor for increased mortality. β-blockers reduce the incidence of SCD in the post-MI population and those with heart failure, again pointing towards increased sympathetic tone as the arrhythmogenic factor. In the electrophysiology laboratory, isoprenaline, a β-agonist, is used to enable the initiation of both supra-ventricular and ventricular arrhythmias. It is likely therefore, that this increase in sympathetic activity in the morning is responsible for the excess of events.

Given that sympathetic activity is known to influence cardiac repolarisation, and therefore the QT interval, it is possible that these patients, the majority of whom have structural heart disease, exhibit an abnormal increase in sympathetic activity in the early morning. Yi et al (Yi et al. 1999) studied QT dynamics in patients with and without SCD following myocardial infarction and compared the grouped hourly values of QT/RR slopes and extrapolated QT intervals at a standardised heart-rate of one second. They demonstrated increased mean hourly QT/RR slopes and relatively prolonged QT intervals in the SCD victims relative to both the MI survivors and the normal controls.

Our data would appear to support the influence of sympathetic activity as being responsible for the morning excess of VT and VF, as the morning peak is not seen in those subjects on beta-blockers. Assessment of the short term changes in early morning QT/RR dynamics is necessary to assess whether abnormal changes occur during this 'dangerous' time of the day.

Chapter 10

Short Term Changes In The Continuously Assessed Early Morning QT/RR Relationship In Cardiac Arrest Survivors: Influence Of Cardiac Sympathetic Activity

10.1 Introduction

In the previous chapter a clear circadian variation in the incidence of sustained ventricular tachyarrhythmias relative to non-sustained VT was elicited in a group of patients with implantable cardioverter defibrillators. When the subjects were divided into two groups according to whether they were taking beta-blockers, a morning excess of arrhythmias was seen only in those subjects not on beta-blockers.

Having demonstrated in earlier chapters that the repolarisation abnormalities in heart failure and hypertrophy are abnormal and progressive, and that chronic beta blockade has a beneficial influence over the rate dependence of QT, we hypothesised that there may be short term repolarisation abnormalities in the morning during the transition period from sleep to becoming ambulant.

It is well known that the 'corrected' QT (QTc) interval is longer during the night, and that this is due to the influence of the autonomic nervous system (Bexton and Vallin and Camm 1986). Beta-blockers have been shown to reduce the rate dependence of QT and also to prolong the QT interval slightly (Merri et al. 1992).

Due to the problems associated with hysteresis and QT adaptation lag, which have been discussed at length in previous chapters, it has proved difficult to obtain accurate assessments of the short term changes that occur at specific intervals, such as those preceding arrhythmias, or in this case, on awakening. In this chapter, using data

collected from the ICD group in the previous chapter, we assess the short-term changes in QT relative to heart rate and compare them to healthy controls.

10.2 Hypotheses

The primary hypothesis is that changes in the relationship between the QT interval and heart rate occur in the early waking hours in patients with a history of ventricular arrhythmias. These abnormalities are likely to be sympathetically mediated and therefore attenuated by beta-blockade. This information may provide insights into the mechanisms of arrhythmogenesis with particular reference to cardiac repolarisation.

10.3 Subjects and Method

Patients recruited into the study in the previous chapter underwent 24h ambulatory ECG recordings. Standard exclusion criteria for QT interval analysis were applied, namely the presence of conduction abnormalities, the presence of bradycardia pacing, atrial fibrillation and very frequent ventricular ectopics. A total of eighty-three 24h recordings were made, of which forty-one were suitable for continuous assessment of the QT/RR relationship. Where recordings were commenced / terminated during the period of interest, data was considered to be circular and continuous (Yi et al. 1999). Recordings from 20 age and sex matched healthy controls were also assessed for comparison. The ICD patients were divided into two sub-groups according to whether they were taking chronic beta-blocking therapy (BB). The characteristics of the ICD patients are laid out in table 10.1.

Table 10.1: Patient Characteristics

Values are means (SD).

	ICD patients (no β-blockers) n=25	ICD Patients (β-blockers) n=16
Age	56 (14)	55 (12)
Sex	4 female	2 female
Previous myocardial infarct	68%	81%
Primary arrhythmia	11%	0%
ARVD/HCM/DCM	12%	20%
Ejection fraction	29% (16%)	31% (16%)
NYHA class	1.6 (0.7)	1.8 (0.7)
Amiodarone	4/25	2/16

10.2.1 Method for assessment of dynamic changes in the QT/RR relationship

The recordings were analysed using the previously described method for dynamic assessment of the QT/RR relationship. From the 24h graphic display of the continuously measured parameters, the time of patients' waking was determined as the point at which the RR interval was seen to decrease in the morning, which usually occurred between 0700h and 0800h. The timing of baseline measurements was 30 minutes prior to this point. From studying 24h printouts of QT and RR' data, it appeared that the changes in the repolarisation characteristics took place within the first 90-120 minutes after waking, and then reached a new steady state about one hour after this. For this reason, and taking into consideration the peak incidence of

arrhythmias between 9 and 10 am (roughly one to two hours after most people rise), values of RR, QTo, slope and J were then measured with on-screen callipers at baseline (30 minutes prior to waking), two hours after this to give a peak value and a further two hours later. This gave a total of three points which were felt to suitably cover the period when an excess of arrhythmic events occurred in the previous chapter. All measurements were performed by an observer blinded to patient group and medical therapy. Absolute values of RR, QT, Slope and J were compared between the three time points and also between the groups by unpaired t-tests. QT/RR curves were constructed from mean group values of QTo and J for each of the time-points.

10.4 Results

10.4.1 Sleeping Characteristics

The healthy volunteers showed a significantly longer RR interval than the ICD patients, irrespective of whether they were taking β-blockers or not. The β-blocker subgroup had a longer RR interval than those not on this medication. During sleep the patient groups had relative prolongation of QTo. The use of β-blockers did not appear to produce any further lengthening of QTo, perhaps due to lower sympathetic activity during sleep. There was no significant difference in either slope or J between any of the three groups during sleep. In summary, this would appear to indicate that although repolarisation is prolonged in the group of patients with a history of cardiac arrest, there was no difference in the rate dependence of repolarisation.

10.4.2 Waking hour repolarisation characteristics

The absolute values of the parameters and the relative changes were compared separately. On waking, all subjects showed a decrease in the RR interval. This was most marked in the healthy volunteers. Patients on beta-blockers showed a reduced shortening of the RR interval relative to those not (–255 vs -393 ms, $p<0.005$). There was a paradoxical lengthening of QTo in both the ICD groups, although this was most marked in the group not taking β-blockers compared with a shortening of QTo in the healthy volunteers (+31 vs –10 ms, $p=0.01$). The group on β-blockers showed a small but significant increase relative to the healthy volunteers (+5ms vs –10 ms).

10.4.3 Two-hour control period

In all three groups, RR interval increased, indicating a slowing of heart rate after the initial early morning peak. QTo shortened further in the HV group (-10ms) . Both ICD groups showed a shortening of QTo. S and J returned towards nocturnal values during this period.

The described differences between groups and time points are laid out in tables 10.2 and 10.3 below. The absolute values of RR, QTo, Slope and J at each time point are seen in figures 10.1 – 10.4).

10.2 a

ICD Patients (no β-blockers) vs Healthy Volunteers		
	Delta 1 **HV NBB**	**Delta 2** **HV NBB**
RR	-393 vs –360 (p=NS)	111 vs 207 (p=0.06)
QTo	**-10 vs 31** **(p< 0.0001)**	**-4 vs –31** **(p<0.005)**
S	**0.052 vs 0.121** **(p<0.001)**	**-0.022 vs –0.105** **(p= 0.001)**
J	**0.025 vs 0.213** **(p<0.0001)**	**-0.051 vs –0.189** **(p<0.0001)**

10.2 b

ICD Patients (on β-blockers) vs Healthy Volunteers		
	Delta 1 **HV BB**	**Delta 2** **HV BB**
RR	**-393 vs –255** **(p<0.005)**	111 vs 137 (p=NS)
QTo	**-10 vs 5** **(p=0.05)**	-4 vs –12 (p=NS)
S	0.052 vs 0.059 (p=NS)	-0.022 vs –0.061 (p=NS)
J	**0.025 vs 0.12** **(p=0.01)**	-0.054 vs –0.11 (p=NS)

10.2 c

ICD Patients (no β-blockers) vs ICD Patients (on β-blockers)		
	Delta 1 **NBB BB**	**Delta 2** **NBB BB**
RR	**-360 vs –255** **(p<0.01)**	180 vs 137 (p=NS)
QTo	**31 vs 4** **(p=0.01)**	-31 vs –12 (p=0.07)
S	**0.121 vs 0.06** **(p<0.01)**	**-0.105 vs –0.061** **(p <0.05)**
J	**0.213 vs 0.120** **(p<0.05)**	-0.189 vs –0.113 (p=NS)

Table 10.2 a-c
Absolute changes in parameters in the QT-RR relationship at the three time-points. Significant differences are indicated in bold. Both patient groups Absolute changes in the parameters of the QT-RR relationship. Delta 1 is the change from sleeping to waking, and delta 2 is the change from 2h post waking to 4h post waking. Significant differences are indicated in bold.

10.3 a

ICD patients (not on β-blockers) vs Healthy Volunteers			
	Asleep HV NBB	**Awake** HV NBB	**2h later** HV NBB
RR	**1126 vs 1043 (p<0.05)**	733 vs 683 (p=NS)	844 vs 779 (p=NS)
QTo	**425 vs 447 (p<0.05)**	**415 vs 472 (p<0.0001)**	**408 vs 437 (p<0.005)**
S	0.14 vs 0.15 (p=NS)	**0.19 vs 0.38 (p=0.05)**	0.15 vs 0.17 (p=NS)
J	0.34 vs 0.31 (p<NS)	**0.36 vs 0.54 (p<0.0001)**	0.31 vs 0.31 (p=NS)

10.3 b

ICD Patients (on β-blockers) vs Healthy Volunteers			
	Asleep HV BB	**Awake** HV BB	**2h later** HV BB
RR	1126 vs 1133 (p=NS)	**733 vs 878 (p<0.0003)**	**844 vs 1037 (p<0.0005)**
QTo	**425 vs 455 (p<0.05)**	**415 vs 457 (p<0.0001)**	**408 vs 452 (p<0.0001)**
S	0.136 vs 0.15 (p=NS)	0.19 vs 0.21 (p=NS)	0.15 vs 0.16 (p=NS)
J	0.34 vs 0.29 (p=NS)	0.36 vs 0.39 (p=NS)	0.31 vs 0.29 (p=NS)

10.3 c

ICD Patients (on β-blockers) vs ICD patients (not on β-blockers)			
	Asleep NBB BB	**Awake** NBB BB	**2h Later** NBB BB
RR	**1043 vs 1133 (p<0.05)**	**683 vs 878 (p<0.0001)**	**779 vs 1037 (p<0.005)**
QTo	447 vs 455 (p=NS)	472 vs 457 (p=NS)	437 vs 452 (p=NS)
S	0.153 vs 0.157 (p=NS)	0.38 vs 0.21 (p=NS)	0.17 vs 0.16 (p=NS)
J	0.31 vs 0.28 (p=NS)	**0.54 vs 0.39 (p<0.01)**	0.31 vs 0.29 (p=NS)

Table 10.3 a-c
Absolute values of parameters in the QT-RR relationship at the three time points. Significant differences are indicated in bold. Both patient groups showed a significantly greater increase in slope and J compared to the healthy volunteers, and again this was less in those patients receiving β-blockers. Significant differences are highlighted in bold.

Figure 10.1: Absolute Values of RR at each of the three time points for each group

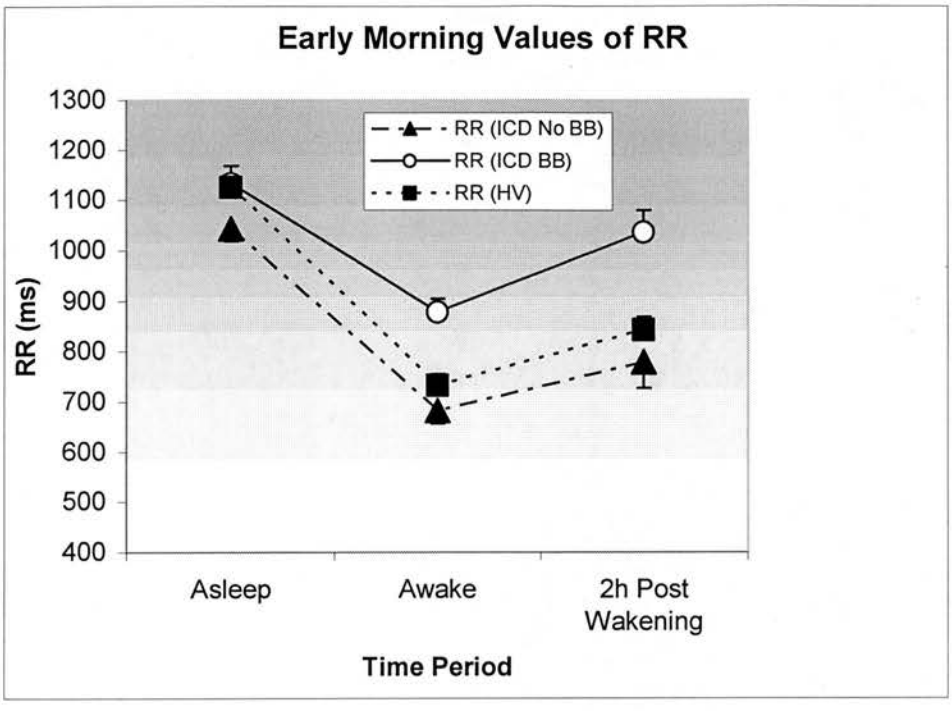


Figure 10.2: Absolute values of QTo at each of the three time-points for each group

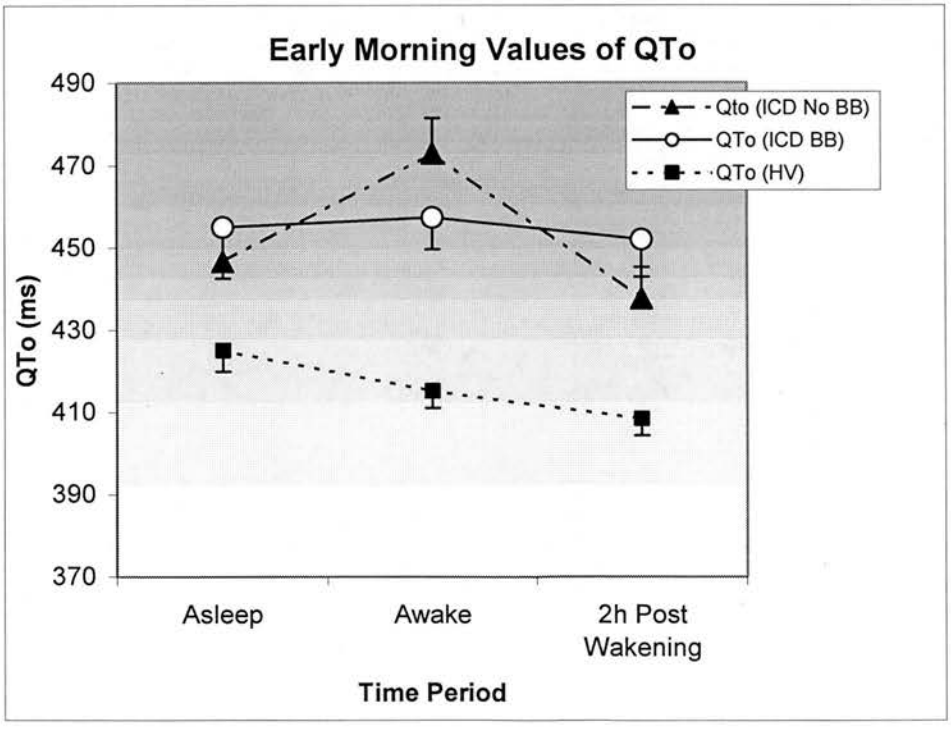


Figure 10.3: Absolute values of Slope at each time point in the three groups

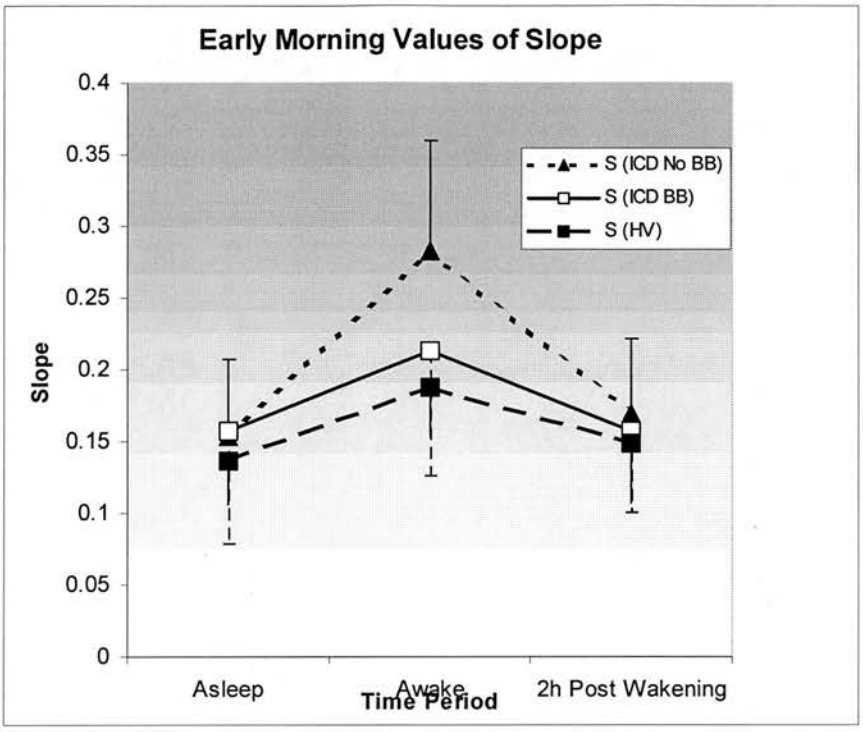
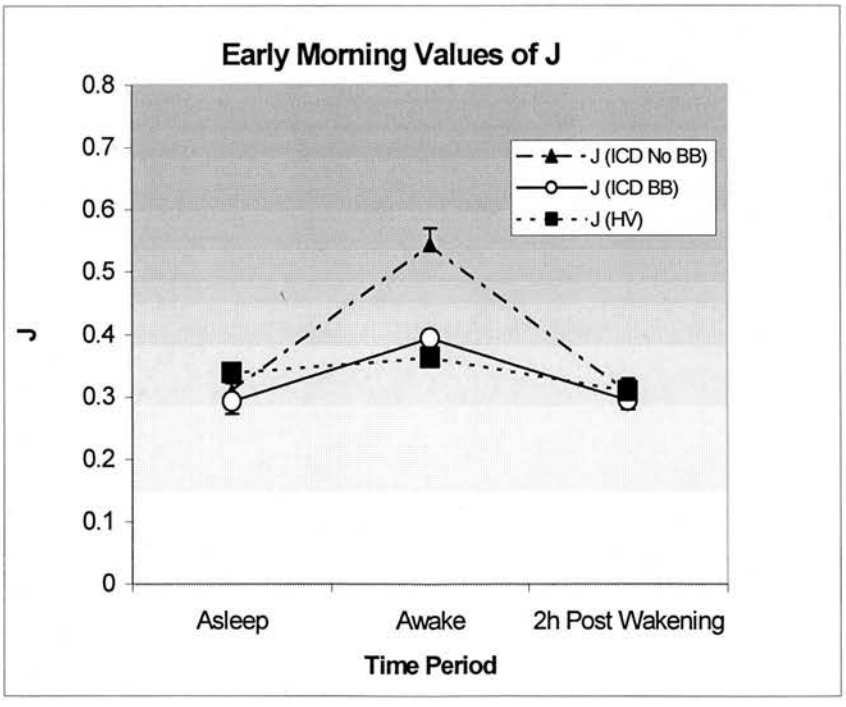


Figure 10.4: Absolute values of J at each time point in the three groups



10.5 Discussion

10.5.1 Changes in heart rate

From the data, several differences between the groups have come to light. The most obvious and expected abnormality is the damped heart rate response on waking in the group of patients taking β-blocking agents. During sleep, there is lower sympathetic activity, although in patients with severe congestive cardiac failure, elevated sympathetic tone is felt to be present throughout the day and night (Panina et al. 1995, Saul et al. 1988). Our population consisted mainly of patients with previous myocardial infarction although symptoms of heart failure and impairment of ventricular function were not marked. The reduced increases in heart rate is indicative of the inability of cardiac sympathetic activity and circulating catecholamines to exert their normal effect due to the sympathetic antagonism from the beta-blockers.

10.5.2 Changes in the relationship between QT and heart rate

In earlier chapters, we have shown that the repolarisation characteristics of patients with heart muscle disease such as those with cardiac failure or HCM have abnormally prolonged QT intervals but also an increase in the rate dependence of QT (using J as a rate-independent marker). There is also evidence that these abnormalities progress with severity of the underlying condition.The results in this section suggest that the same is true of patients with a history of previous cardiac arrest. This population differs in that they have heterogeneous conditions and are symptomatic to varying degrees. In the previous chapter we examined the circadian variation in the incidence

of malignant arrhythmias requiring ICD intervention in this group and uncovered a morning excess of events between 9 and 10am, corresponding to a period approximately one to two hours after waking or rising. This chapter has focussed on the repolarisation dynamics at that time to assess whether an abnormal or exaggerated response is seen at that time of day.

One of the most striking abnormalities present on many of the recordings from the defibrillator patients was an increase in the value of QTo in the group not on β-blockers. This was accompanied by a significant increase in slope and J. In contrast, the rise in QTo and J was much smaller in the β-blocked group. Other investigators, using hourly estimates of the QT/RR slope (Fei et al. 1994) or Bazett's corrected QTc (Yi et al. 1999) have also shown changes in the 'waking hour' QT/RR relationship to be more marked in similar patient populations. As we have previously discussed, limitations of these methods restrict the classification of the whole QT/RR curve and complicate the continuous assessment of the relationship.

We postulated in an earlier chapter that increased sympathetic activity was responsible for the increased rate dependence of QT seen in heart failure. This was upheld by the later chapter in the ICD study of 24h repolarisation characteristics that showed a slight increase in the length of QTo in patients on β-blockers but a reduction in J. The results in this section would appear to support the role of sympathetic activity in the morning surge in slope and J. Other investigators have studied the circadian variation in the levels of circulating catecholamines and showed

that noradrenaline (NA) levels peaked at 0800h, and a smaller peak was also seen in adrenaline levels (Kong et al. 1995). The fact that β-blockade in our population resulted in a dampening of the rise in QTo and J points to a surge in sympathetic activity and circulating catecholamines on rising as being responsible.

In the early morning there is a complex interaction between autonomic changes, circulating factors and changes in activity and posture that result in changes in heart rate and repolarisation. This makes it difficult to appreciate what is truly occurring in the relationship between QT and RR. The elevated value of QTo that is seen to occur in the ICD group would imply that the excessive risk of arrhythmias at this time of day in this group might be due to a prolongation of ventricular repolarisation. It is easier to comprehend what is actually occurring when the QT/RR curves are plotted for each of the three time-points in the three groups (Figure 10.5-10.7). When this is done, it can be seen that in the healthy control group, although heart rate changes occur that are comparable with the ICD group (no β-blockers), there is no significant change in the overall relationship between QT and RR. When these curves are compared with the ICD (no-βB), we can see that although QTo increases, the increase in J is actually responsible for a shorter QT at the peak heart rate than would have been seen at the same heart rate if the QT/RR relationship had not changed from the relationship seen during sleep. There is therefore a **shorter** QT and therefore shorter refractory period at that time of day. In the β-blocked subjects, a smaller increase in QTo occurs, along with a substantial increase in J. If heart rate acceleration had not been blunted by β-blockers, this group would also have had a relatively short QT and refractory period.

Figure 10.5

Waking hour changes in the QT/RR relationship in healthy volunteers. The large circles represent the RR interval for each of the three time points. These curves have been generated by taking the values of QTo and J at each of the time points (30 min pre, 120 mins post and 240 mins post waking), and using them to calculate the values of QT at various RR intervals by using the formula $QT = QTo.RR^{J}$.

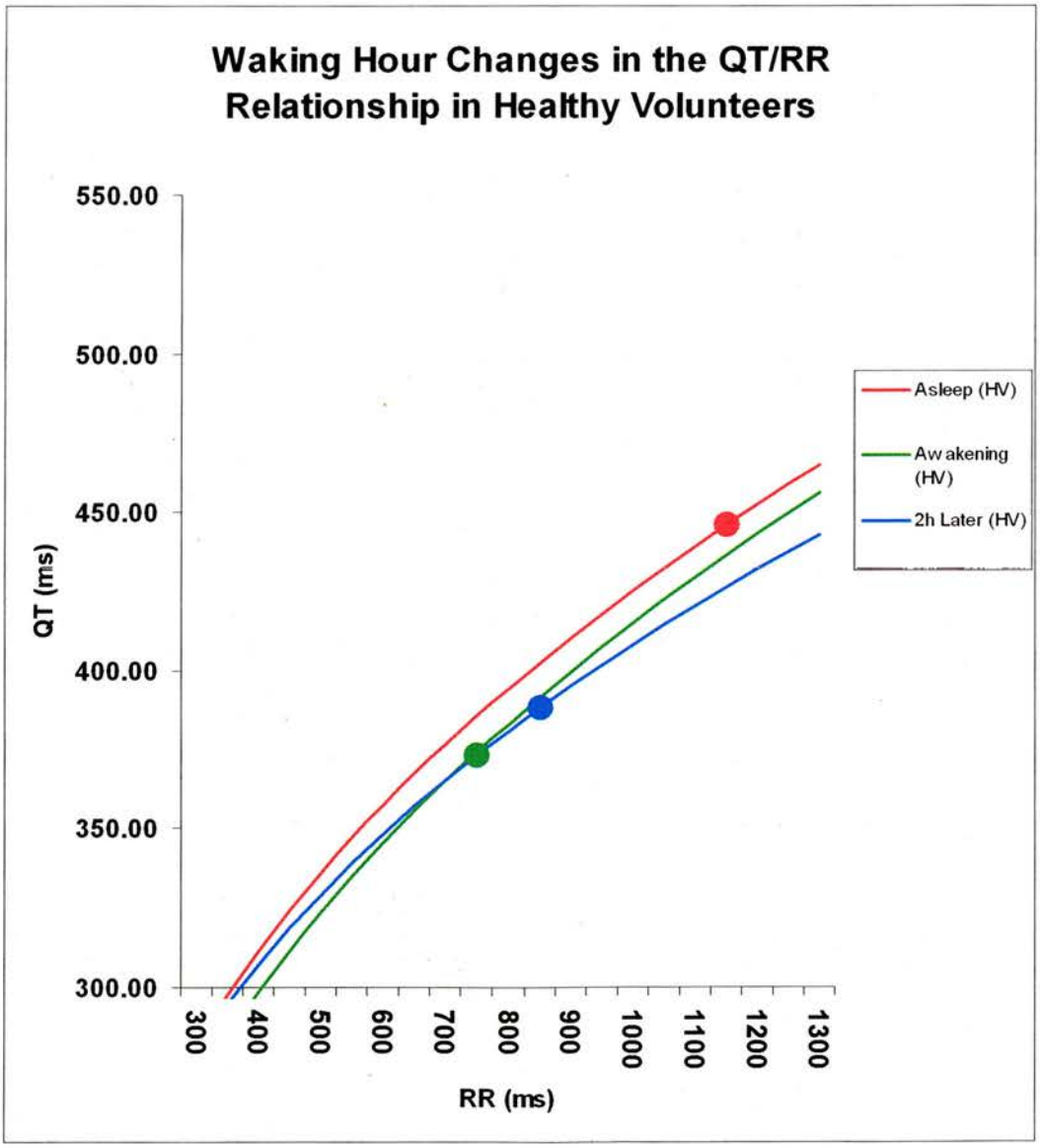


Figure 10.6

Waking hour changes in the QT/RR relationship in patients with a prior history of cardiac arrest. Curves and symbols are as in figure 10.5. In contrast to healthy volunteers, the morning rise in heart rate is associated with a paradoxical rise in the extrapolated value of QTo (QT at an RR interval of 1000ms). When this is viewed in the context of the curve, it can be seen that due to the rise in slope and J, the QT interval at the higher morning heart rate is actually shorter than it would have been at that rate on the 'sleeping curve'.

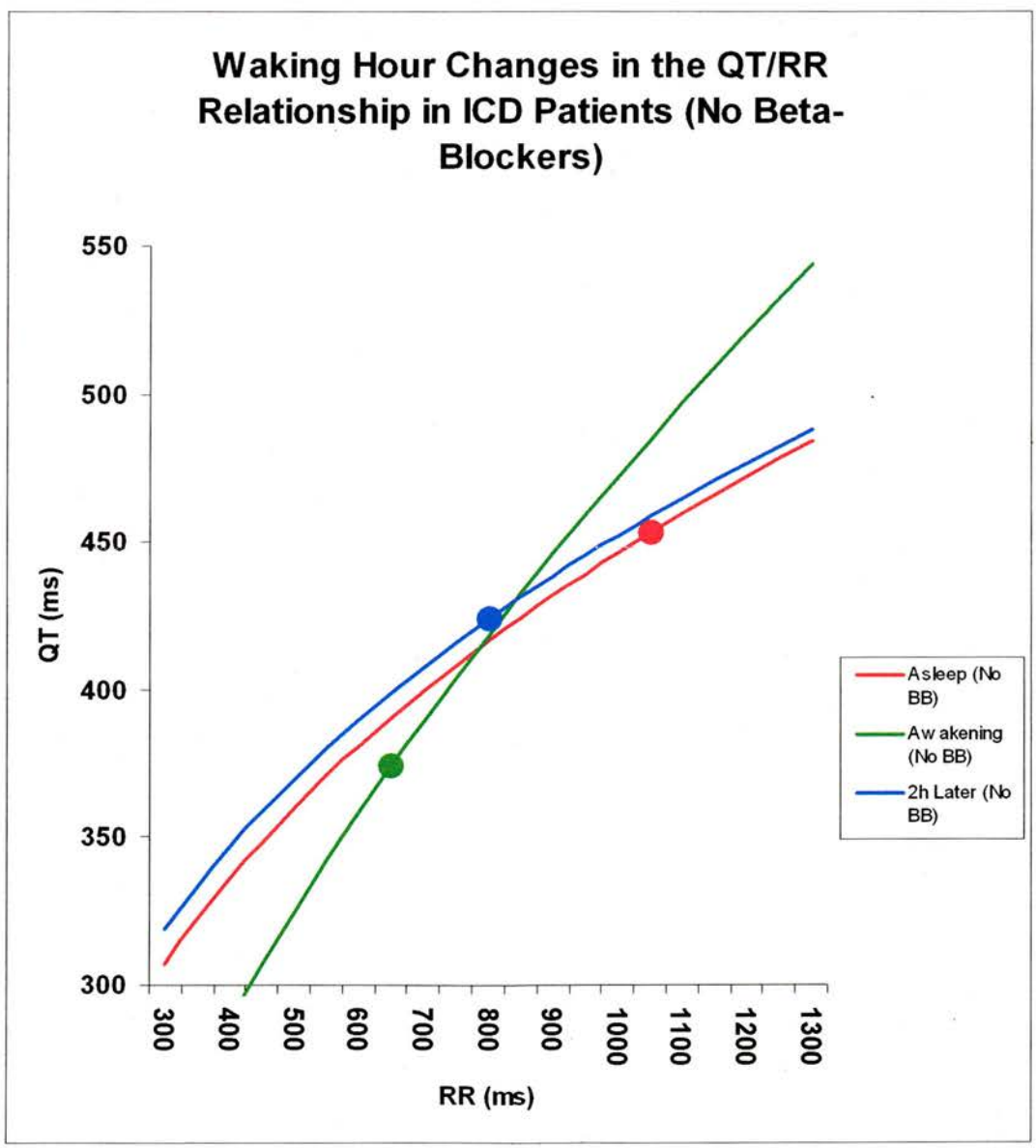
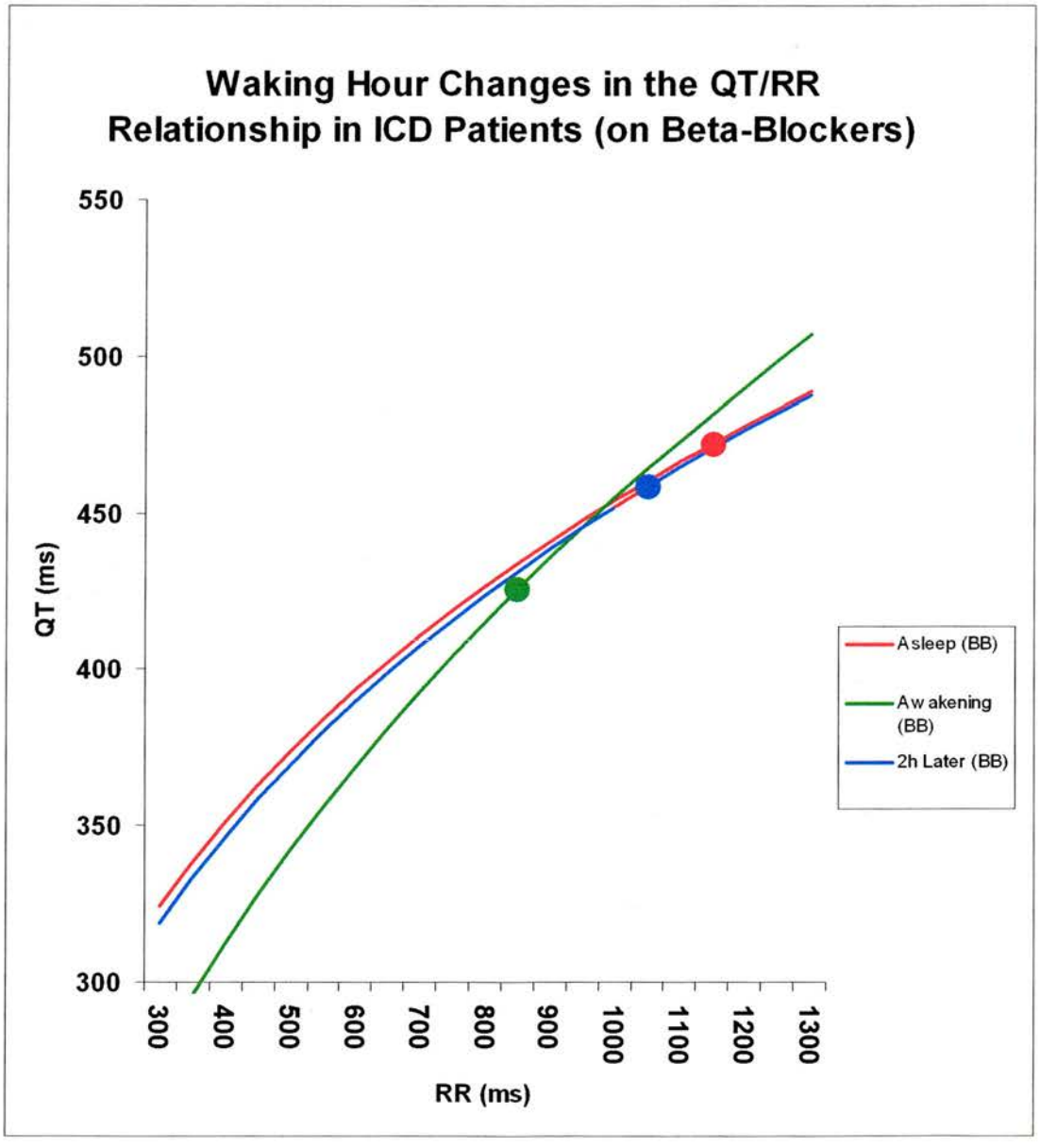


Figure 10.7

In the ICD population receiving chronic β-blocker therapy, less separation of the curves is seen, although there is a tendency towards shorter QT intervals at higher heart rates. The rise in heart rate is considerably less in this group on wakening (as shown previously in figure 10.1). No significant change in the QT is observed, largely because heart rate has not increased as much.



The explanation for the observed differences between ICD patients and healthy subjects is that the majority of these patients had ischaemic heart disease, left ventricular impairment and/or heart failure. As in the previous chapters, we have shown that the QT/RR relationship seems to worsen with the degree of heart failure. In these patients, the abnormalities that we are observing may reflect an enhanced cardiac sympathetic influence, and the fact that to increase cardiac output in the morning, there is more reliance on increased sympathetic drive rather than withdrawal of parasympathetic tone (which is the case in healthy volunteers).

Singh et al (Singh et al. 1998) studied a post-infarct population three to five days following infarction and showed a similar early morning (within one hour of waking) surge in the slope of the QT/RR relationship which was less marked in those patients on β-blockers. 24h recordings were analysed using a semi-automated system for measurement of QT and RR and QT/RR slopes were constructed using all analysable beats for the preceding hour. As in our study, data were aligned according to the patients hour a wakening. The QT/RR slopes measured in their study were significantly lower than reported here, and this may be due to the methodology employed and lack of compensation for hysteresis as discussed in chapter 4. They hypothesised that the abnormal increase in the QT/RR slope may reflect an instability of repolarisation and disturbances in autonomic tone.

Other investigators have studied the effective refractory period (ERP) in patients with permanent pacemakers with no evidence of cardiac disease. In this group the

refractory period was measured non-invasively via the permanent pacemaker. The refractory period showed significant circadian variation, being 4% longer 4h before waking, and reached its shortest duration one to two hours after waking (3.5% shorter than 24h mean). This variation seemed to correlate best with epinephrine levels when normalised for time of wakening. The circadian variation in ERP was abolished by β-blockade.

Another study (McLelland et al. 1990) assessed the inducibility of ventricular arrhythmias and the refractory period in patients at electrophysiological study according to the time of day of testing. They found no difference in the refractory period and concluded that circadian variation in ERP may not play a role in the morning excess of arrhythmias. However, the EP lab is a highly artificial environment, and there are external and internal influences at work, not least patient anxiety during the test, which might abolish any genuine differences present.

The use of beta-blockade in the post-myocardial infarction population is well established and proven to provide mortality benefit (Beta-blocker Heart Attack Trial Research Group 1982, Norwegian Multi-center Group 1981). A sub-study analysis of the mortality data from the The Beta-Blocker Heart Attack Trial (Peters 1990) specifically examined the differences in the incidence and circadian variation in SCD in those receiving the non-specific β-blocker propranolol with the control group. The incidence of sudden death was reduced in the treatment group. In addition, the morning excess of SCD in the placebo group (38% of all SCD) was significantly

reduced in the treatment arm (24%). Excluding this period, there were nearly equal numbers of death at other times of day.

More recently, β-blockers have been proven to be beneficial in the treatment of patients with ischaemic and dilated cardiomyopathy (Merit-HF Study Group 1999, CIBIS-II Investigators and Committees 1997, Australia/New Zealand... 1997). Although an improvement is seen in markers of severity of heart failure such as ejection fraction, NYHA class, heart rate variability and biochemical markers of neuro-humoral activation, and a corresponding reduction in the incidence of death due to worsening of heart failure is seen, much of the mortality benefit is actually due to a reduction in the incidence in sudden cardiac death, approaching 50% in most of the large studies. Studies assessing the circadian variation in heart failure have suggested that the classical morning excess of SCD is reduced or absent in this population (Carson et al. 2000). Regardless of this, given that patients with heart failure are known to have increased sympathetic activity throughout the day, it is highly likely that sympathetic activity plays a role in the initiation and maintenance of arrhythmias. However, as already discussed in the chapter on heart failure, prolonged repolarisation and triggered activity is a postulated mechanism of initiation of malignant ventricular arrhythmias in these patients, particularly in the absence of an identifiable anatomical substrate for macro-reentry.

10.5.3 Implications Of The Observed Repolarisation Abnormalities And The Connection To Arrhythmic Death

We have shown that in this population of patients with predominantly ischaemic, post-myocardial infarction related VT or VF, the morning excess of arrhythmias appears to correspond with an abnormal shortening of the QT interval. In contrast, the incidence of non-sustained arrhythmias is more evenly distributed throughout the 24h period. This would suggest that the shorter repolarisation (and therefore refractory period) seen at higher heart rates may be altering the properties of potential re-entrant circuits to allow maintenance of VT, and/or degeneration into VF. This is comparable to the techniques employed in the EP lab by cardiologists to induce arrhythmias with infusion of the β-agonist isoprenaline. Our data suggests that one mechanism by which beta-blockers are effective, at least in terms of repolarisation dynamics, is by blunting the heart rate increase as well as preventing the rise in rate dependence of the QT interval.

10.5.4 Implications for future research

By continuously assessing the QT/RR relationship, it is possible to see that the changes occurring in the morning are in fact gradual and progressive over more than an hour, as seen in figures 10.2 – 10.4. The technique employed offers greater temporal resolution than methods which cannot compensate for hysteresis.

The increase in QTo which can subsequently be shown to correspond with a shorter QT interval when heart rate is taken into consideration highlights the limitations of quoting a 'corrected QT' as a stand-alone assessment of cardiac repolarisation in the dynamic setting. One must also describe the curves on which the points lie in order to understand what is truly occurring.

The assessment of dynamic repolarisation characteristics in this way may be providing a more direct insight into the action of the autonomic nervous system on the ventricular myocardium. The ability to constantly monitor changes over short periods may prove important in the assessment of patients with coronary artery disease or cardiac failure in specific situations such as exertion.

Many agents, whether anti-arrhythmic drugs or drugs with an incidental tendency to cause prolongation of repolarisation (such as anti-psychotics, macrolide antibiotics or anti-histamines), may also cause changes in heart rate, or can be used in patients who are tachycardic (e.g. the febrile patient with pneumonia). Measurement and 'correction' of the QT interval using standard formula is likely to give misleading results, particularly if a generic formula is used (such as Bazett's).

The subject is even more complex for class three agents such as Sotalol. Let us consider d-Sotalol, the dextro-isomer of racaemic sotalol, which has less than 2% of the β-blocking activity of the laevo-isomer. This drug causes QT prolongation by blocking inward potassium currents (IKr). It does so by binding to closed potassium

channels. This results in greater prolongation of QT at lower heart rates as more molecules bind during the longer diastolic period (phase 4 of the action potential). If we were to arbitrarily say that at a heart rate of 60bpm, a fixed dose of sotalol induces a 40ms lengthening of QT as measured on a resting ECG. It would be possible to apply Bazett's correction formula and estimate the QT at a heart rate of 30 bpm or 130 bpm. However, we have made two assumptions which we know to be incorrect- firstly that a subjects QT/RR relationship has a square-root relationship with heart rate (or J=0.5), and secondly that the relationship will follow the same relationship at 30 or 130 bpm, which we also know to be incorrect due to the rate dependent binding properties of the drug. It is comparable to measuring QT at a heart rate of 60 bpm after 50mg of IV sotalol, and then giving a further dose of sotalol and expecting the QT interval to still be the same.

If we are to prevent arrhythmias in patients with re-entrant circuits that are dependent on a short refractory period, we need to prolong action potential and/or the refractory period, or render a cell less excitable. The SWORD (Waldo and Camm and de Ruyter 1996) and CAST (The et al. 1989) studies have highlighted the risk of pro-arrhythmia in the use of class I and III agents in relatively low risk subjects. The risk of pro-arrhythmia is related to the binding characteristics of these agents and the relative lack of effect at high heart rates. In the CAST study in particular, the excess of deaths appeared to be at least in part due to an increase in nocturnal death, when RR and QT intervals are at their longest (Peters et al. 1994). The advantage of defibrillators is that they do nothing unless it is required of them. The disadvantage of drugs is that they

act all the time, and many are less effective during tachycardias as they produce less change in the action potential at high heart rates, and perversely are far more potent when least needed (when heart rate is low), creating a situation where long-QT mediated arrhythmias may occur. The Holy Grail of arrhythmologists is an 'intelligent' drug which exerts minimal effect at normal heart rates, and then binds aggressively to receptors during tachycardias. This positive use dependent property has not been found in any agent under development to date, but is likely to come in the future.

Amiodarone is a special case worth mentioning. Although it exerts most of its anti-arrhythmic effect through class III action potential prolongation, it also has non-receptor mediated anti-adrenergic activity. In addition, it appears to have less reverse use dependence than other class III agents. It may be these properties which have rendered it arguably the most effective agent at our fingertips. If it were not for the unfortunate side-effect profile, it would surely be more widely used.

10.6 Conclusions

The 'high-risk' early morning period when arrhythmias are more likely to occur is associated with an abnormal increase in the rate dependence of QT in cardiac arrest survivors. A paradoxical increase in the estimated QTo is seen but constructed QT/RR curves demonstrate that the QT interval is abnormally short at this time. The shortening of QT is abolished by β-blockade, largely due to a modification of the

heart rate response. This may explain the mechanism of anti-arrhythmic action of β-blockers in these patients. These findings highlight the problems of correcting the QT interval for heart rate, and cast further doubt over the use of rate correction formulae for making comparisons in the QT interval of patients under varying physiological and pathological conditions.

Chapter 11

24h Repolarisation Characteristics in Patients with Implantable Defibrillators: Do Repolarisation Characteristics Predict Events?

11.1 Introduction

The two previous chapters have been concerned with the circadian variation and the early morning changes in repolarisation in a group of patients with implantable defibrillator devices. Having demonstrated that there is an early morning excess of episodes of sustained ventricular arrhythmias, we hypothesised that this was due to the increase in sympathetic activity. On wakening, considerable changes in the repolarisation characteristics were seen, and these were attenuated by β-blockade.

In this chapter we assess the clinical variables and the 24-hour repolarisation characteristics in the patients who had Holter recordings of sufficiently high quality to assess whether any of these parameters serve as predictors of events.

11.2 Hypotheses

Having demonstrated repolarisation abnormalities in heart failure and HCM, we hypothesised that in a population known to be at risk of SCD, we might expect the mean 24-hour characteristics of repolarisation to be abnormal. We compare the patients who, over a one year follow up period received therapies from their ICD with those who were event free.

11.3 Subjects and Method

Of the 83 patients in whom Holter recordings were performed, 41 were of sufficient quality for 24-hour assessment of the QT/RR relationship. Ejection fraction, NYHA class, and medication were recorded. Patients taking class III agents were also excluded for this section as they would have a significant effect on repolarisation and possibly reduce events due to the anti-arrhythmic action. This resulted in exclusion of three patients from the No-Therapy group, and one patient from the Therapies group. All patients were followed up for one year and the number of episodes of non-sustained (NSVT) and sustained VT were recorded. The patients were divided into two groups according to whether or not they received therapies from the defibrillator. The characteristics of the patients are laid out in table 11.1. The significance of differences in values between groups was assessed by χ^2 testing for categorical data and t-testing for continuous data.

11.4 Results

The characteristics of the patients with recordings suitable for analysis are given in table 11.1. It can be seen from the table that there was no significant difference in age, sex or ejection fraction between groups (although significantly more patients had structurally normal hearts in the 'event' group), raising the possibility that this skewed the ejection fraction data. Corroboration for this is provided by the fact that 70% of patients in the 'no-event' group were taking ACE-inhibitor therapy. There

was a slightly greater incidence of episodes of NSVT in the event grouping, suggesting this as a possible marker of risk of further sustained events.

Table 11.1 Population and group characteristics

	No events	Events	Overall	p value
Number	21	16	37	N/A
Sex	4 female	4 female	8 female	p=NS
Age	55	52	53	p=NS
Ejection Fraction	32	34	33	p=NS
NYHA Class	1.75	1.46	1.63	p=NS
% IHD	73%	57%	67%	**p<0.001**
% Primary VT/VF	9%	19%	14%	**p<0.04**
ACE Inhibitors	70%	40%	57%	**p<0.001**
Beta-blockers	40%	40%	40%	p=NS
NSVT	50%	64%	56%	**p<0.05**

The results of the 24h QT analysis are detailed in table 11.2. It shows that the group of subjects suffering arrhythmic events during follow up had lower values of slope and J, although these did not attain statistical significance. QTo was also significantly shorter in the event group at the 5% level.

Table 11.2 Results are expressed as mean (SD). Significance is assessed by students unpaired t-test. Significance is defined as a p value of less than 0.05.

	No Events	Events	p value
RR (ms)	904 (118)	920 (123)	p=NS
QT (ms)	428 (35)	416 (32)	p=NS
QTo (ms)	458 (28)	436 (32)	**p<0.05**
S	0.185 (0.06)	0.15 (0.05)	p=NS
J	0.372 (0.10)	0.33 (0.09)	p=NS
SD of J	0.18 (0.09)	0.08 (0.13)	p=NS
pooled r	0.80 (0.1)	0.79 (0.11)	p=NS

11.5 Discussion

11.5.1 Repolarisation and Events:

It is perhaps slightly surprising, in light of the previous chapters, that the patients with events have repolarisation characteristics that we would consider more "normal" than those who escaped events. We must bear in mind, however, that the population is very different from those with heart failure or HCM. The majority of these patients had arrhythmias secondary to ischaemic heart disease, the majority having had a remote myocardial infarction, many with subsequent aneurysm formation. The mechanism of arrhythmia in this group is more likely to be macro-reentry. Prolongation of the QT interval in this situation is not necessary to sustain the arrhythmia, although triggered beats may well cause initiation. It is more likely that in

this situation, *dispersion* of repolarisation or the presence of delayed impulse propagation through or around the aforementioned anatomical barriers are more relevant. When this is considered, it becomes slightly less disappointing that the repolarisation characteristics do not appear to be predictive of arrhythmic events. Significantly more patients in the 'event' group had structurally normal hearts. The mechanisms for their arrhythmias are often unclear. It may be that transient ischemia or, for unknown reason, transient electrophysiological abnormalities, may be responsible, as many subjects with witnessed out-of hospital arrhythmic events will be non-inducible at subsequent electrophysiological testing.

This study was ambitious in that it attempted to establish whether arrhythmic risk could be determined from a high risk population followed for one year. Although over one-hundred subjects were recruited, the numbers of recordings available for direct comparison of repolarisation dynamics has dwindled to less than 40. This is a disappointment and has reduced the potential of the study.

11.5.2 Observations in Diagnostic Groups

Given that all these patients are considered to be at ongoing risk of SCD, it is valid to consider these patients as being at higher risk than a patient with an equivalent clinical diagnosis and symptoms who has not had a cardiac arrest. If we consider each diagnostic group separately, some insight can be gained regarding the relevance of the QT/RR relationship, and hopefully guide further studies. These data are subsequently summarised in figure 11.1.

Group 1:

Patients with Previous Cardiac Arrests and Structurally Normal Hearts

There were five subjects in this group with tapes of sufficiently high quality for analysis. Four were female. None was taking amiodarone or β-blockers. They had an average RR interval of 815ms, QT of 384ms and QTo of 420ms. Slope and J were 0.17 and 0.35 respectively. In summary, the individuals with 'structurally normal hearts' also appeared to have, at least in terms of 24h averages, entirely normal repolarisation characteristics. Given that these patients may also be non-inducible at the time of electrophysiological study, it may be that, at times, changes in repolarisation occur that trigger or predispose to arrhythmias.

Group 2:

Patients with severely impaired LV function.

Out of the 37 ICD patients, seven had a primary diagnosis was of heart failure and had an ejection fraction less than 15%. One patient had idiopathic dilated cardiomyopathy and the others had ischaemic cardiomyopathy due either to previous infarction or severe coronary artery disease with chronic ischemia. The mean values in this group were far more abnormal than those with normal hearts. Mean RR interval was 852 ms and QT 434ms. QTo was considerably elevated at 482 ms and both slope and J were high (0.255 and 0.470 respectively). Four of the five subjects were taking β-blockers which as we have shown, will tend to reduce both slope and J. These values, although not statistically significant, are higher than the average for our

heart failure population in chapter 5 (QTo = 472ms, J = 0.44). These findings tend to suggest that repolarisation abnormalities may play a role in sudden cardiac death in the heart failure population.

Group 3: Hypertrophic cardiomyopathy

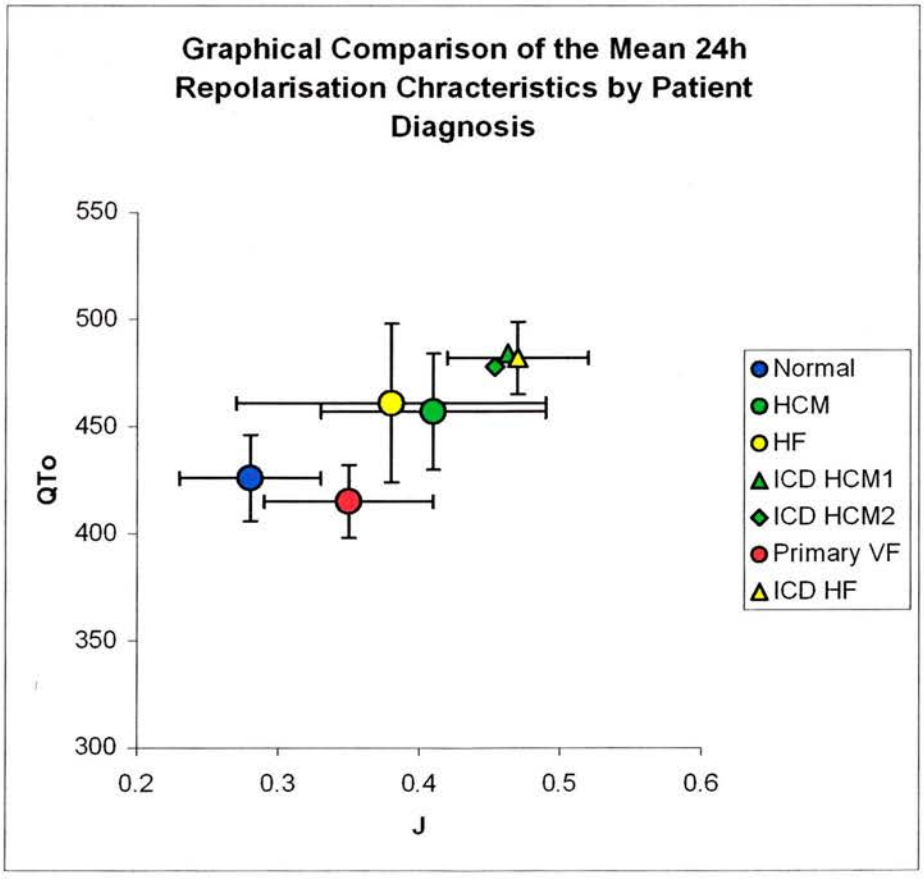
Unfortunately there were only two patients in this population with recordings suitable for analysis. They are however interesting and deserve special comment:

Patient 1: A 39 year-old lady was diagnosed with HCM following family screening after the death of several family members at an early age. She was assessed at a tertiary centre for HCM research where it was revealed that she had a troponin gene mutation which, statistically, carries a high risk of sudden death. Despite no previous history of arrhythmias, and the fact that she was asymptomatic, it was felt that there was sufficient evidence to warrant defibrillator implantation for primary prevention. She underwent 24h Holter analysis for our study, and the results were in the upper ranges of our HCM study population (QTo = 484ms, J = 0.463), compared with population means from chapter 6 (QTo = 457±27, J = 0.412±0.08).

Patient 2: A 43 year old gentleman was diagnosed with HCM after being successfully resuscitated from VF at a football ground where he was spectating. An ICD was implanted, and during follow-up he has had four further episodes requiring therapy. His mean 24-hour repolarisation characteristics were also abnormally high, even for an HCM patient (QTo = 478, J = 0.554).

Figure 11.1

The repolarisation characteristics of the subgroups from the populations studied are represented graphically by plotting the mean 24H QTo against mean 24h J. The values for the ICD subgroups are more abnormal than the corresponding patient population without defibrillators. The exception to this is those subjects diagnosed with a primary arrhythmia with structurally normal hearts (labelled primary VF). X and Y error bars represent one standard deviation of the mean. The study population of patients with hypertrophic cardiomyopathy are indicated by the green circle, whereas the two patients with hypertrophic cardiomyopathy who have ICDs (ICD HCM1 and ICD HCM2) are indicated by individual green markers. For the general heart failure population studied, a yellow circle has been used, whereas the subgroup of ICD patients with a primary diagnosis of heart failure are indicated by a yellow triangle, with associated error bars.



11.6 Conclusions

It was known before embarking on this ambitious project that the interpretation of results would be difficult. Data on dynamic QT abnormalities in different patient groups was not available at the outset, and the heterogeneous nature of the population meant that it was less likely that we would find that patients with events would fall on the side of more abnormal repolarisation. The previous chapters which looked at the timing of arrhythmic events and the changes in the QT/RR relationship at that time of day suggest that the majority of the patients in this particular population have events at a particular time and for a reason. Ischemia and increased sympathetic activity are just two possible reasons for this.

The data presented in this and the previous chapter would seem to suggest that there may be two distinct types of patients – those in whom the arrhythmias are mediated by re-entry, ischemia and sympathetic activity, and those in whom abnormal repolarisation plays a part. This will hopefully encourage further studies in the fields of heart failure and hypertrophic cardiomyopathy. We plan to undertake both a retrospective and prospective study of HCM patients in collaboration with Dr Fananapazir at the NIH. The patients with idiopathic ventricular arrhythmias had entirely normal 24h repolarisation dynamics on the day tested, but no comment can be made about the response to adrenergic activity. It would seem unlikely however that prolongation of repolarisation is the culprit.

Chapter 12

Discussion and Implications for Future Research

12.1 Technical Considerations

This body of work has been concerned with the application of a newly developed method for the analysis of the relationship between the QT interval and the inter-beat or RR interval. As with many new techniques there are inevitably problems encountered along the way. In the first section, data is presented on the reproducibility of 24-hour averages in healthy volunteers, and we also highlighted the impact QT adaptation lag has on the QT/RR relationship when assessed over a short time frame.

One of the points raised in this chapter was that the signal quality is paramount if we are to be able to comment reliably on the underlying relationship. Although 2-channel recorders were used, frequently only one channel would be suitable for analysis. In healthy volunteers, this was often the apical channel CM5. In heart failure, it could be either, although in at least fifty percent of the recordings, neither was suitable. This was usually due to low signal amplitude and subsequent unfavourable signal to noise ratio, or, as is often the case in patients with severe left ventricular impairment or arrhythmias, frequent ventricular ectopy.

Patients with hypertrophic cardiomyopathy posed different although equally challenging problems. Again, although the magnitude of the complexes was sufficiently good for analysis, the morphology of the T wave could at times cause

erroneous measurement of T_{end}. This, as stated in an earlier chapter, is due to the algorithm for T_{end} detection, which offers significant advantages in other respects, but can result in the analyser being misled into measuring Q-T_{apex} rather than Q-T_{end} . Fortunately, due to the fact that the operator can continuously monitor the Q and T_{end} markers during playback, erroneous results can be avoided, but sometimes at the expense of excluding a subject from analyses. It is anticipated that this problem will be largely resolved as hardware and software refinements currently in the late stages of development become available. This would include the function of being able to define a 'region of interest' during playback that would start after T_{apex} and end shortly after T_{end}. By setting this, it would force the analyser to ignore any slope changes prior to the onset of the region of interest, reducing the likelihood of measurement of Q-T_{apex}.

12.2 Implications for the Assessment of the QT/RR Relationship in HCM and Heart Failure

The main aims of this thesis were to establish whether abnormalities existed between not just the QT interval, but also the overall relationship between QT and RR intervals in health and disease. Considerable differences are seen in both heart failure and hypertrophic cardiomyopathy. These illnesses share several common features, in particular the cellular hypertrophy in response to impaired contractile function, and also in the unpredictable episodes of sudden arrhythmic death. In both of these groups

we have shown associations between stage of disease and abnormal repolarisation characteristics, suggesting that the 'electrophysiological remodelling' is a progressive phenomenon. In light of the well known relationship between prolongation of the QT interval and polymorphic VT, it is tempting to conclude that this is likely to be associated with an increased risk of arrhythmia. In view of this, steps are underway to analyse prospectively collected data from a long-term follow up study in hypertrophic cardiomyopathy to assess whether prognostic information with regards to sudden cardiac death are present.

12.3 Short-term Assessment of Repolarisation Dynamics

The latter sections of the thesis studied first the circadian distribution of arrhythmic events in patients with a previous out-of-hospital cardiac arrest. A significant circadian variation of sustained arrhythmias was seen relative to non-sustained VT The morning excess of sustained arrhythmias was not seen in patients on beta-blockers, implicating increased early morning sympathetic activity as the arrhythmogenic trigger. The majority of these subjects had re-entrant monomorphic VT secondary to ischaemic heart disease. Assessment of changes in the QT/RR relationship at around this time in the morning showed that a significant change occurred with an increase in the steepness of the curve as indicated by a rise in J. This equated to an overall greater shortening of QT and refractory period, implicating an abnormal or excessive response to autonomic changes in the morning. It is, of course, possible that having impairment of the left ventricle, autonomic balance is towards sympathetic preponderance with lower vagal tone. In order to increase heart rate and

cardiac output to match metabolic demands, less can be achieved by withdrawal vagal tone, and greater sympathetic activity is required. This would appear to be borne out by the reduced changes seen in the group taking β-blockers. Nonetheless, it would appear to link changes in the relationship between repolarisation and heart rate with arrhythmic events in this group.

The short-term changes in this study have also highlighted the limitations of 'rate correction' of QT. The majority of formulae for correcting the QT interval for heart rate were developed using resting ECG data. It is now recognised that these formulae are not applicable during exercise and we have clearly demonstrated with this method that progressive changes in the relationship occur, particularly at times of increased sympathetic activity. This should discourage us from the arbitrary use of such formula in dynamic situations, particularly at high heart rates.

12.4 Short-term versus 24-hour Measurements

The main body of this thesis quotes 24-hour values of repolarisation characteristics. The latter section on the ICD subset looked at the early morning changes which coincided with the arrhythmic episodes. The subsequent chapter looked at the 24-hour characteristics in the same population and showed that the patients with events actually had more 'normal' 24-hour values than those without.

While logic would dictate that if a mean 24-hour QT-RR characteristic is more abnormal, one might expect more events. This would appear to hold true for the data on heart failure patients and HCM, and there is limited evidence that this may be the

case from subgroup analysis. However, it may not be appropriate for the patients with re-entrant arrhythmias. The ICD group was composed largely of such patients, and there was a striking circadian variation in events. The majority of these patients had re-entrant VT which is dependent on refractory periods and conduction velocities, factors which are determined by autonomic activity and the presence of ischaemic areas in the ventricle.

It may be that the study of repolarisation dynamics using this method can be employed in different ways in different conditions. In patients with previous myocardial infarction, the assessment of short-term episodes where metabolic stress is present, such as during exercise tolerance testing, may be more fruitful. In this situation there is increased sympathetic activity, potentially ischemia and also changes in acid-base balance and temperature. This may yield interesting results and identification of 'at-risk' patients may be possible. In contrast, patients who are thought to be more prone to the 'triggered activity' type of VT/VF may be more usefully stratified by measurement of longer-term repolarisation characteristics. In these subjects, if arrhythmias mediated by prolonged repolarisation are hypothesised, one would expect that the overall 24-hour 'burden' of repolarisation may be predictive. Indeed, as mentioned earlier, the circadian variation in SCD is less striking in these groups in some studies.

12.5 Assessment of Pharmacologically Induced Repolarisation Changes

In chapter eleven I discuss a theoretical model of what might be seen in patients given a class III anti-arrhythmic agent with 'reverse-use-dependent' properties at varying heart rates. The advantages of the current method of assessing repolarisation change in the setting of drug testing are twofold. Firstly, as the QT-RR relationship is assessed for each individual, comparisons between placebo and active agents can be made more accurately. We have shown that in healthy volunteers, the 24h characteristics are highly reproducible but also that there is a considerable variation, not only in terms of QTo but also J. The mean values of J are also considerably lower than that used in Bazett's formula, the most widely applied correction method. The use of Bazett's formula is therefore liable to produce errors when heart rate varies significantly from 60 beats per minute.

The second advantage is that the overall relationship, expressed in terms of QTo and J can be computed continuously and independently of heart rate. This may lend itself in particular to agents which have non-linear binding characteristics or rate modifying effects. The search for anti-arrhythmic agents with positive-use dependence is continuing, but can be difficult to assess. While initial work on novel agents is always carried out on isolated cells and animal models, with ligand binding characteristics established in the laboratory, at some stage it needs to be assessed in man. Anti-arrhythmic efficacy can be tested either in the electrophysiology laboratory, or by long-term follow-up studies. These are invasive and expensive. A method that allows

reliable assessment of repolarisation changes at varying heart rates may prove to be a very useful and cost effective means to test these agents.

At present, the method is being used in two diverse settings to evaluate it's potential contribution. Firstly, we are performing a study in collaboration with the Scottish Poisons Unit in the Royal Infirmary of Edinburgh which aims to assess the repolarisation changes in patients who have taken overdoses of substances known to prolong the QT interval and provoke arrhythmias. These fall into three main groups:

1. Tricyclic Antidepressants (e.g. Amitryptyline)
2. Antipsychotic Agents (e.g. Chlorpromazine)
3. Anti-histamines. (e.g. Terfenadine)

As many of these agents will also induce tachycardia due to intrinsic sympathomimetic activity or secondary to hypotension, the rate correction of QT is problematic and prone to error if Bazett's or other correction formulae are used. In addition, the repeat measurement from 12 lead ECGs is laborious, expensive and time consuming and therefore less likely to be done. If we are able to continuously track changes in the overall relationship, it may be possible to incorporate such a method into monitoring facilities which will enable the medical staff to determine when a significant risk is present and also to monitor the improvement, enabling more accurate prediction of when a patient's risk of arrhythmia has passed.

We are also analysing recordings from a pharmaceutical company in the late stages of phase II clinical trials where infusion of a novel pharmaceutical agent was noted to induce prolongation of the corrected QT. Unfortunately it also causes significant tachycardia which complicates accurate rate correction. On analysis of dynamic recordings, it is seen that the baseline measurements of J are around 0.3, and QTo is well within the normal range. During the infusions, continuous assessment shows that there is in fact very little change in J or QTo. The perceived prolongation of the corrected QT is actually due to the overestimation of J in the standard rate correction formula. This is similar to the findings in the 'waking hour' repolarisation changes, where we demonstrated that quoting QTo alone is misleading. It also emphasises that using the wrong value of J and quoting QTc alone is even worse.

The disadvantage of applying a new method in these settings is that normal ranges will need to be established, new markers of arrhythmic risk will need to be sought and some method of assessing combinations of QTo and J in terms of arrhythmic risk will need to be developed. Nonetheless it would appear to be an ideal use of this method.

12.6 Conclusions

I have been fortunate to be the first person to use this method for dynamic QT analysis. The research contained in this thesis has yielded many interesting results, underlining the importance of abnormal repolarisation and also changes in the QT/RR relationship in many conditions. This method also appears to offer many of the

solutions to the problems associated with 'correcting' QT for heart rate. There are now, however, even more interesting questions to be answered. Whenever a project is embarked upon, the goals are often relatively well defined, but as more of the pieces of the puzzle fit together, the puzzle merely becomes bigger and the end is never reached.

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Appendix

Articles:

Lang, CCE, Flapan,AD, Neilson, JMM. *The impact of QT Lag Compensation on Dynamic Assessment of Ventricular Repolarisation: Long term reproducibility and the importance of lead selection.* Pacing and Clinical Electrophysiology, 2001; 24: 366-373.

Lang, CCE, Flapan,AD, Neilson, JMM. *Abnormalities of the Repolarisation Characteristics of Patients with Heart Failure Progress with Symptom Severity.* Annals of Non-invasive Electrocardiology. In press, July 2004.

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Lang CCE, Neilson JMM, Flapan AD. *Abnormal Dynamic QT/RR Relationship In Patients With Heart Failure As Determined From 24 Hour ECG Recordings.* PACE, April 2000, 23, No. 4, Part II, 709. Presented at the North American Society of Pacing and Electrophysiology, Washington DC, May 2000.

Lang CCE, Neilson JMM, Flapan, AD. *Dynamic Repolarisation Abnormalities Distinguish Between Patients with Heart Failure and Normal Subjects.* European Journal of Heart Failure. Presented June 2000 at Heart Failure 2000, Venice, Italy.

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Lang CCE, Mohiddin S, Flapan AD, Fananapazir L. *MRI measurements of Left Ventricular Hypertrophy Correlate with Prolongation of Rate Corrected QT on Holter Recordings*. Presented. North American Society of Pacing and Electrophysiology, May 2001

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OMPUTER COLUMN

he Impact of QT Lag Compensation on Dynamic ssessment of Ventricular Repolarization: eproducibility and the Impact of Lead Selection

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NG, C.C.E., ET AL.: The Impact of QT Lag Compensation on Dynamic Assessment of Ventricular Repolarization: Reproducibility And The Impact of Lead Selection. *In cardiac disease, abnormalities exist the rate-corrected QT interval and the relationship between QT and heart rate. The QT/RR relationship known to be dynamic and show circadian variation. The availability of automated methods for measement of QT and RR intervals allows monitoring of the QT/RR relationship and may provide insights o arrhythmia onset. Using a method for analyzing 24-hour recordings that incorporates beat-by-beat QT d RR measurement and an automated mechanism for compensating for lag in adaptation of QT to anges in RR, the authors evaluated the impact of lag compensation on assessment of the QT/RR relanship, reproducibility, and the effect of lead selection in 15 normal subjects. The QT/RR relationship continuously estimated from the lag compensated data over a 5-minute scrolling time frame. The relanship is expressed as an exponential formula, $QT = QTo \cdot RR^J$ where QTo is the QT interval at a standrdized RR interval of 1 second and J is a variable exponent. We found that the use of lag compensation nificantly improves the mean 24-hour correlation between QT and RR data (r = 0.87 vs 0.65). The 24ur mean of QTo and J were highly reproducible (coefficients of variation 2% and 8%, respectively). The an 24-hour QT/RR relationship for the population was $QT = 0.415 \cdot (RR)^{0.32}$. There was a small differce between leads in QTo and J. Compensating for QT adaptation lag provides a means of assessing the /RR relationship over long and short periods. This method allows investigation of the effect of acute inventions on the dynamic QT/RR relationship, which has previously been restricted by the presence of hysteresis. (PACE 2001; 24:366–373)*

interval, dynamic, ambulatory, hysteresis

Introduction

Interest in the QT interval has grown ever ce the association between congenital or acred QT prolongation and malignant ventricular ythmias was made.[1] The QT interval is influed by many factors, the most apparent of ch is heart rate. Therefore, it is necessary to ect for this to allow comparison among clinivariables, individuals, or populations. Since 0 when Fridericia[2] and Bazett[3] first indepenly proposed exponential rate correction forlas, many other formulas have been proposed have included linear,[4,5] exponential, [6] and logarithmic models.[7] Controversy exists over the true relationship between the QT interval and the interbeat or RR interval, and much of this may be due to the timing of measurement of the QT and RR intervals. It is well recognized that when heart rate changes, there is a delay in the adaptation of the QT interval to the new heart rate (QT lag).[8–12] For example, if heart rate changes quickly to a new sustained higher rate during sudden exertion, it may take several minutes before the QT interval adapts to the new steady-state heart rate. The converse is also true, such that as heart rate slows, the QT interval will require several minutes to fully prolong to its new steady-state value. Investigators attempt to allow for this when measuring QT at different heart rates, but it may be that the times allowed to reach steady state are inadequate. If this is the case, there will be underestimation of the QT/RR slope.

Recent advances in medical technology now allow automated short- and long-term measurement of the QT interval on a beat-by-beat basis

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m ambulatory electrocardiographic (ECG) ordings. This makes it possible to study the cir- lian variation in the QT/RR relationship and s yielded insights into the possible reasons for increased incidence of arrhythmias early in the rning.[13] Furthermore, analyses of long-term ordings allow the assessment of acute interven- ns such as drug administration on the changes he QT/RR relationship. It has become clear that QT/RR relationship is not constant but varies ring the day, and therefore, when assessing dy- nic long-term recordings, a more flexible thod is needed to describe the QT/RR relation- p and to permit more accurate rate correction.

Caution must be used in analyzing dynamic a precisely because the heart rate is constantly nging and the QT will always tend to lag be- d changes in heart rate. Unless a method is d that allows for this time lag, errors will oc- . One approach to this problem has been to an- ze periods when heart rate has been constant hin a narrow range for several minutes.[14,15] s method can result in loss of large amounts of a when heart rate is changing and decreased poral resolution of observations.

In 1998, Neilson[16] proposed and developed a erent approach to QT/RR analysis that incor- ated a modeled correction for QT lag, thereby wing accurate estimation of the underlying re- onship over even very short intervals. Using t-by-beat QT and RR data, the QT lag is cor- ed by imposing a matching lag to RR data. This rection allowed determination of the slope of underlying, steady-state QT/RR plot and cal- tion of the exponent J in the general relation- : $QT = QTo \cdot (RR/RRo)^J$.

For any point in time, the precise relationship veen the QT and the RR interval is defined by variables QTo (the extrapolated QT at RRo, chosen reference RR interval) and J (the expo- t of the general formula that determines the pe of the curve).

In this study we chose RRo equal to 1,000 ms assessed the 24-hour mean values of QTo and a population of healthy volunteers and com- d the results with and without the use of lag pensation. Spatial differences in QT/RR rela- ship were also examined by comparing the obtained simultaneously from two different leads. We report the reproducibility of the our mean values of QTo and J over a 7-day rval.

Method

Fifteen healthy male volunteers (mean age ears) without a cardiac history and on no ication underwent 24-hour ECG recordings g two-channel 'Tracker 2' recorders (Reynolds Medical Ltd., Hertford, England) on two occasions 1 week apart. Standard bipolar thoracic leads CM5 and CM1 were used. All subjects were asked to abstain from alcohol and follow their normal daily routines on both recording days. One subject was excluded from further analysis due to the presence of frequent supraventricular ectopics. Consent was obtained in all subjects in accordance with the authors' local ethics committee requirements.

The tapes were replayed on a Pathfinder Analyser (Reynolds Medical Limited) that excluded ectopic complexes and those that were significantly distorted by artefact. The analyzer measured each RR interval and its associated QT interval. The T_{end} was measured using the slope method whereby the end of the T wave is determined as being the point at which the current slope of the T wave drops below a predetermined proportion of the maximum slope. The accuracy of the automated QT interval measurement has been independently validated.[17]

Twenty–four-hour files of RR and QT intervals are then processed on a personal computer using a novel technique to determine the QT:RR relationship. The three-stage process is described below.

First, the well-known two component time lag[18,19] with which the QT interval follows changes in RR interval is "compensated" by applying a matching two-component time lag to the RR data. This resynchronizes the QT and RR variations so that when the compensation is correctly adjusted, a screen display of QT against RR no longer shows the characteristic loops due to "QT Hysteresis" but retraces the corresponding part of the underlying steady-state QT/RR curve. This is the curve that would have been traced if RR had changed slowly enough so the effect of the QT delay on the plot would be negligible. During analysis the operator can confirm the absence of "hysteresis loops" and hence correct compensation for the QT lag (Fig. 1).

Second, throughout the analysis, the RR and QT signals are cross-correlated within a moving 5-minute time window that is scrolled through the 24-hour data. As long as the correlation between QT and RR remains high ($r > 0.8$), the slope (S) of the QT/RR plot around each successive (RR, QT) point is computed as the linear regression coefficient in the time window currently centered on that point. Thus, a continuously updated measure of the slope of the QT/RR characteristic curve is generated.

Third, it is found that this slope decreases at longer RR intervals, providing evidence that the steady-state QT/RR characteristic is curved. To avoid the necessity of reporting the value of RR at

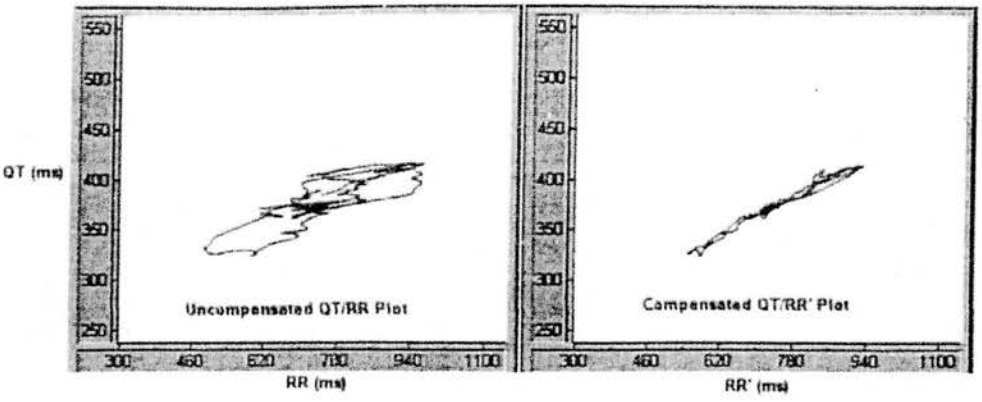


Figure 1. *An example of the QT lag compensation in action. The figure represents a 3-minute excerpt from a 24-hour recording. The left panel is raw QT:RR data. Each QT interval is plotted against the preceding RR interval and each point is connected to the previous one by a line. The right panel is the same QT data, but matching lag has been placed on the RR data and each QT interval is then plotted against the corresponding delayed RR interval, RR'. This has resulted in an improved correlation between QT and RR with accelerations and decelerations in heart rate tracing out one curve. This enables the measurement of the underlying QT/RR relationship as though it were derived from steady-state data.*

ch measure of slope, the simple exponential em-ical formula used by Fridericia[2] and Bazett[3] is opted.

These investigators used $QT = K \cdot RR^{0.33}$ and $= K \cdot RR^{0.5}$, respectively, from which the "Cor-ted QT" has customarily been computed as c (Bazett) = QT / √RR and QTc (Fridericia) = / $\sqrt[3]{RR}$.

These familiar formulas have given rise to ne confusion regarding the correct units for c. To avoid this difficulty the present method s the most general expression: $QT = QTo * (RR/RRo)^J$.

Here QTo is the intercept of the curve with ordinate at RRo, a chosen reference RR inter-, and J is the exponent determining the shape of curve. (Bazett's formula assumes that J is con-nt and equal to 0.5, while the Fridericia for-la is equivalent to adopting a fixed value of 3 for J) In the present method the value of J is tinuously computed from $J = S \cdot (RR'/QT)$, ere RR' is the compensated value of RR.

Statistical Analysis

Recordings were excluded from statistical lysis if they did not fulfill the following crite-data used > 90%, pooled 24-hour QT:RR cor-tion > 0.8, recording duration > 18 hour. A akdown of the number of recordings available ach channel is given in Table I. Of the 14 pairs ecordings, 13 pairs were of sufficient quality assessment of 24-hour reproducibility in one oth channels. When comparing the difference he calculated QT/RR relationship between compensated and uncompensated data, all analyzable channels were used. This produced a total of 35 acquired recordings that were then analyzed with and without lag correction and compared by paired *t*-test. Due to a low yield of high quality recordings in channel 2 (CM1), only 11 tapes were available for comparison of interlead differences when quality criteria were applied. Reproducibility of the technique was assessed by calculation of the coefficient of variation (CV) defined as the standard deviation of the mean difference between recordings, divided by the mean of the population, and expressed as a percentage. Interlead differences were assessed using paired *t*-tests.

Results

The mean pooled 24-hour regression coefficient was 0.86 for compensated data, implying that throughout the 24-hour period the correlation between QT and RR data was high. This contrasts with the correlation for the uncompensated data (r = 0.63). Although the mean pooled correlation for the population is 0.86, for the duration of most of the recordings it is actually much higher, as can be seen in Figure 2, a 24-hour chart from a typical normal subject.

Figure 1 demonstrates the lag compensation in action during a 3-minute excerpt of the playback. The left panel shows raw QT and RR datapoints and the right panel shows the lag correction has been applied. QT is now plotted against the delayed RR intervals (RR'). This increases the correlation between QT and RR.

Table I.

Summary of Suitability of Recordings for Analysis

	Tape 1	Tape 2	Total of Analyzable Recordings	Pairs where both Tape1 and Tape 2 Analyzable in the Same Channel	Total Pairs (either channel)
Channel 1 (CM5)	12/14	12/14	24/28	11/14	13/28
Channel 2 (CM1)	7/14	4/14	11/28	2/14	
Total analyzable recordings	19/28	16/28	35/56		
Pairs where channel 1 and channel 2 analyzable from the same tape	7/14	4/14			
Total pairs (either tape)	11/28				

Breakdown of recordings suitable for analysis by channel and tape number. Where the same channel was available for analysis in both recordings (tape 1 and tape 2) this is used as a pair of assessment of the reproducibility. Where both channels were of sufficient quality in the same recording (tape 1 or tape 2), the pair is used to assess the effect of using different leads on mean 24-hour values. All recordings of sufficient quality, irrespective of channel or tape number, were combined to assess the effect of applying lag compensation on the estimated QT/RR relationship.

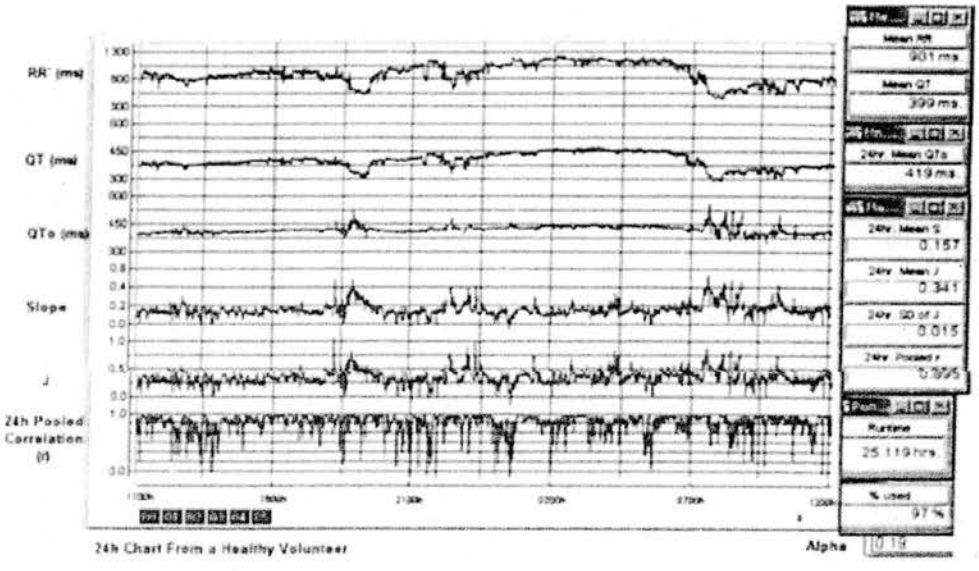


Figure 2. *A 24-hour printout of compensated QT and RR (RR'), along with the parameters S and J used to describe the QT/RR relationship. Recording was commenced at 1100 hours. It can be seen that while the patient is sleeping (approximately 2330–0700 hours), there is a slight lengthening of QTo with reduction in the variation seen during waking hours. Slope is also seen to decrease slightly, secondary to a longer RR interval, meaning the QT intervals are on the flatter portion of the QT/RR curve. There is a slight reduction in J during sleep relative to waking hours. On waking, there is a sharp rise in QTo, slope and J that coincides with the rapid shortening of the RR interval. The figures on the right-hand side are mean 24-hour values.*

Table II.

Comparison of Lag Compensated Versus Uncompensated Data

n = 35	RR (ms)	QT (ms)	QTo (ms)	S	J	24-hour SD of J	24-hour Pooled r
Uncompensated	901.4	396	408	0.06	0.127	0.009	0.650
	(86.65)	(23.6)	(19)	(0.01)	(0.019)	(0.0028)	(0.08)
Compensated	901.4	396	415.74	0.146	0.320	0.018	0.87
	(86.65)	(23.6)	(17)	(0.02)	(0.04)	(0.014)	(0.06)
P value	N/A	N/A	< 0.001	< 0.001	< 0.001	< 0.001	< 0.00001

All results are 24-hour mean (standard deviation). Correlation between QT and RR is less good when data is uncompensated. There are significant differences in the estimated mean 24-hour QTo, S, and J.

The mean 24-hour results for compensated ıd uncompensated values are given in Table II. To is significantly shorter when data is uncom-ensated. Lack of compensation also results in a duction in the mean 24-hour slope which, in rn, reduces the observed 24-hour mean J. Con-ructed QT/RR plots using mean 24-hour com-ensated and uncompensated results are shown in gure 3.

The reproducibility of the method was as-ssed by comparing mean 24-hour values. Where o channels were of sufficient quality in both cordings, both channels were included in analy-. Table III gives the mean differences and CV for ch of the parameters. The standardized QT at an interval of 1,000 ms (QTo) is highly repro-cible despite a 7% variation in mean 24-hour . Slope and J also had a low CV (11% and 7%, pectively).

In 11 recordings, both channels were of suffi-ntly high quality to allow assessment of the im-ct of lead selection on the value of the parame-s. Table IV details the differences between annel 1 (CM5) and channel 2 (CM1). The slight ference in mean 24-hour RR is due to automatic ting of noisy segments that differ according to channel analyzed. There was a 15-ms differ-ce in QT and a 13-ms difference in QTo be-een channel 1 and channel 2 with the CM5 lead ving a longer mean 24-hour QT and QTo. The 15 lead also tended to have a steeper slope and her J.

Discussion

Compensating for QT lag by delaying RR data proves the correlation between QT and RR, as denced by the high pooled 24-hour correlation fficient. This demonstrates the ability of the thod to compensate for hysteresis and enable mation of the underlying QT/RR relationship ng short-term nonsteady-state data. QT lag mpensation also corrects for the underestima-n of slope that occurs with beat-by-beat assess-ment of QT dynamics. Other researchers have shown that when nonsteady-state data is used, the QT/RR slope is less steep.[15]

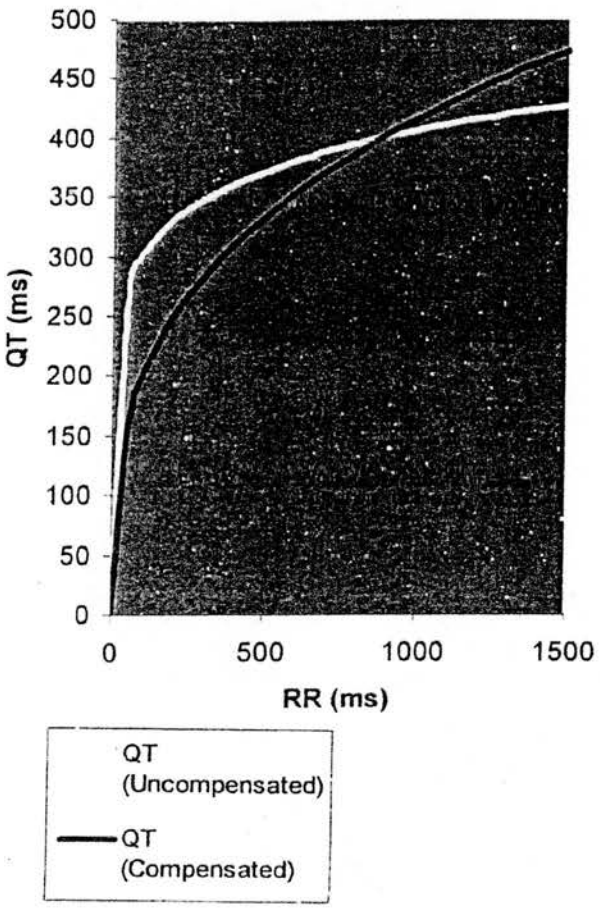


Figure 3. *Demonstration of the different curves derived by analyzing QT/RR data over a scrolling short time frame. The uncompensated data gives a lower value of QTo. Mean slope and the exponent describing the curve (J) are also lower for the uncompensated data, giving the light grey curve.*

Table III.

Reproducibility of Parameters for Paired Recordings 1-Week Apart

n = 13	RR (ms)	QT (ms)	QTo (ms)	S	J	24-Hour Pooled r
Mean (SD)	895.65 (89.61)	396.11 (21.63)	415.9 (17.33)	0.152 0.022	0.33 (0.03)	0.893 (0.044)
Mean difference (SD)	15 (66.63)	5.1 (12.1)	5.0 (8.11)	0.0041 (0.017)	0.00829 (0.025)	−0.012 (0.046)
CV	7.44%	3.04%	1.95%	11.1%	7.42%	5.2%

The coefficient of variation (CV) is calculated as the standard deviation (SD) of the differences between recordings, divided by the mean value for the population.

The use of a short (5-minute) time window of- s high temporal resolution for assessment of the derlying QT/RR characteristic.

We found that J varies constantly throughout day, usually within a fairly narrow range, as licated by the small average 24-hour SD of J ble II). However, occasional peaks and troughs occur. An example of circadian changes in J be seen in Figure 2. Whether the degree of iation in J, which can be described by the 24- ır mean SD of J for the recording, reflects the ree and frequency of alteration in factors such he autonomic nervous system remains to be n.

In contrast, QTo seems to vary little with this thod, showing a trend to be longer at night, ıer than varying constantly. For consistency, in ure 1, the same scale is used for QT and QTo. in, occasional peaks and troughs are seen in o, most commonly on waking in the morning ortly after 0700 hours in this subject). These nges may reflect the interaction of numerous ors that are known to affect QT independently ate, namely posture, autonomic tone, and cir- ating factors like corticosteroids and catecholamines. The peaks on waking may be linked to the increased incidence of arrhythmias seen in the early hours of the day. Acute arousal events have been shown to be important triggers in the initiation of ventricular arrhythmias in some patients with the congenital long QT syndromes.[20,21]

Even in this small study, there was a considerable spread of 24-hour mean values of QTo and J across the population. The range of mean 24-hour QTo was from 384 ms to 448 ms, although this has been accentuated by analyzing channels 1 and 2 together. Equally, there was a spread of values for J (0.28–0.382).

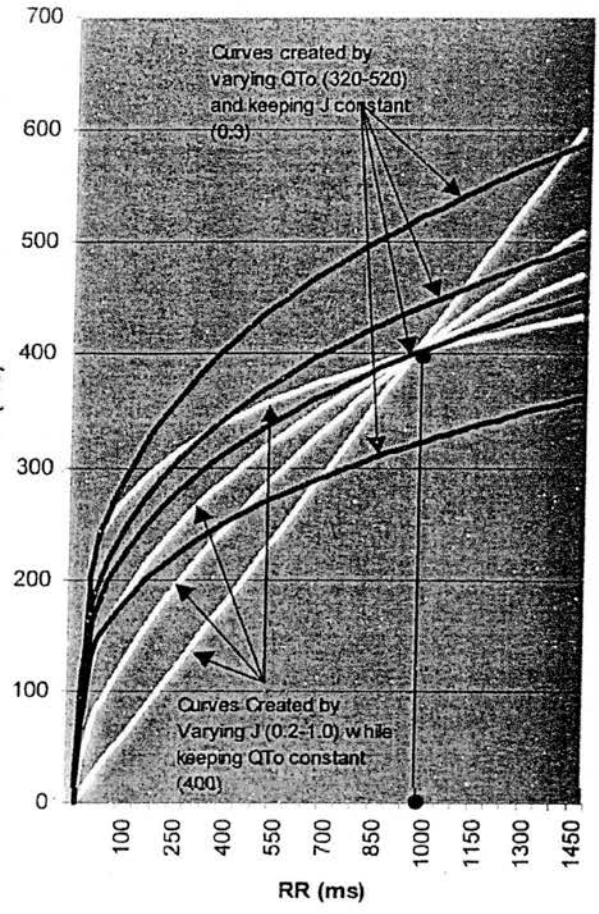
Despite the constantly changing nature of J, and the range of values seen in QTo and J across the population, the intrasubject mean 24-hour values of both are reproducible. The 2% CV in QTo corresponding to an 8-ms difference between recordings is small when compared with the observed 17-ms SD of QTo across our population. A similarly small difference is seen in J. This suggests that genuine differences exist between individuals, and that the 24-hour mean QT/RR curve is reproducible under stable conditions. The high reproducibility of this new method suggests that

Table IV.

Interlead Differences in 24-Hour Parameters

n = 11	RR (ms)	QT (ms)	QTo (ms)	S	J	24-Hour Pooled r
Channel 1 (CM5) Mean (SD)	902 (107)	405 (21.2)	424 (14.9)	0.151 (0.03)	0.324 (0.01)	0.89012 (0.03)
Channel 2 (CM1) Mean (SD)	894 (97)	389 (31.3)	409 (19.7)	0.142 (0.026)	0.313 (0.021)	0.83 (0.05)
Mean difference	9.5 (18.02)	15.1 (16.2)	13.2 (16.4)	0.0094 (0.010)	0.0132 (0.019)	0.0663 (0.060)
P Value	NS	< 0.05	< 0.05	< 0.05	0.06	< 0.05

Paired *t*-test used to assess the significance of difference between leads.



ure 4. *The effects of varying values of QTo and J on overall QT/RR relationship. Abnormal values of QT occur despite a "normal" QTo. At long RR intervals, J is greater than normal, QT will be prolonged. nversely, at higher heart rates, if J is low, QT intervals l be prolonged relative to mean values.*

en small intrasubject changes in the QT/RR re-onship could be detected.

The variation of J with time and among sub-ts highlights the problems associated with the rch for a universally applicable rate correction mula, as discussed by others.[22] Figure 4 is a structed plot of families of curves created by ying QTo or J. It can be seen that as QTo or J ies, significant differences in QT occur over a ge of heart rates. It can be seen that under cer-circumstances, a "normal" QTo at a standard-d heart rate of 60 beats/min can be associated h abnormal QT intervals at fast or slow heart s if J is significantly different from normal. By cribing the QT/RR relationship in terms of QTo J, a more informed judgement can be made as whether the QT/RR relationship is abnormal.

Lead selection has been shown in this study roduce a small but significant difference in observed QT and QTo. There is also a small difference in the estimated values of S (0.01) and J (0.01). Estimation of the spatial dispersion of repolarization by measurement of the QT dispersion has generated a huge number of publications over the years. Controversy exists over whether the measured dispersion in QT intervals is truly a reflection of spatial differences in repolarization or due the geometrical projection of the T wave on the ECG[23,24] and there have been numerous editorials on the use and significance of QT dispersion.[25–27] Whether QT dispersion is real or not, the significance of lead differences in the context of analysis of the QT/RR relationship is unknown. From a technical standpoint, the use of a standardized lead with a low amplitude T wave and an unfavorable signal to noise ratio (S:N) is more likely to provide erroneous results than selecting the lead with the most accurately determinable T_{end}, albeit on a different axis.

Limitations

This study was relatively small and examined only normal subjects. Further work will be required to assess normal ranges and the influence of the patient's sex. As with all methods for the analysis of QT dynamics from ambulatory recordings, the quality of acquired ECG waveforms, in terms of signal quality and the accurate editing out of frequent premature or aberrant beats, is essential. T wave morphology may be abnormal or of low amplitude in many patients with heart disease and ectopy more frequent. This will affect the yield of recordings of sufficiently high quality where accurate T_{end} measurement is possible. In this study, mean 24-hour values are quoted and an average of 72,000 beats was analyzed per recording. A few nonedited abnormal beats are unlikely to influence results. The yield of high quality recordings in this population was good, particularly for the CM5 channel. Individuals were young, slim, and had normal hearts with normal T wave morphology. This is often not the case in clinical practice. It can readily be seen that when analyzing CM1, T waves were of lower amplitude, degrading the S:N ratio so that when this study's selection criteria are applied, the yield drops from $> 90\%$ to $< 50\%$ of recordings suitable for analysis. This finding reinforces the importance of ranking a good T wave morphology over lead position when selecting electrode sites for ECG recordings intended for QT analysis.

Conclusions

This method shows potential for the assessment of the short- and long-term characteristics of the QT/RR relationship in healthy volunteers.

represents a significant change from previous pproaches to the analysis of dynamic recordings that it is the first to use a method for compenting for QT lag. As the QT/RR relationship folws a curve over a broad range of heart rates in nbulatory data, describing the QT/RR characristic in terms of two variables, QTo and J, it removes the need for quoting a slope for each RR interval. It may be well suited to the assessment of the effect of medications on aspects of ventricular repolarization. Further work is required to establish normal values in a larger population and to evaluate differences under nonphysiological circumstances.

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Abnormalities of the Repolarization Characteristics of Patients with Heart Failure Progress with Symptom Severity

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Background: Congestive heart failure is a common condition with high mortality. Many of these deaths are sudden and unexpected. Ventricular action potential, surface repolarization (QT interval), and dispersion of repolarization are prolonged in the failing heart, contributing to arrhythmogenesis and sudden death. We studied the relationship between QT and heart rate (RR interval) from ambulatory recordings using a novel method in patients with ischemic heart disease and varying degrees of left-ventricular impairment (IHD) and compared them to healthy subjects (HS). We compare the degree of abnormality with the functional impairment and ejection fraction.

Methods: Using a previously described automated method for continuous estimation of the QT/RR characteristic that incorporates a correction formula for compensation of QT adaptation lag (VERDA, Del Mar Reynolds Medical Ltd., Hertford, UK), we compared recordings from 41 IHD patients with age-matched HS.

Results: IHD Patients have prolonged 24-hour mean QTo (461 ms vs 426 ms, $P < 0.01$), and abnormal rate dependence relative to controls (24-hour mean slope: 0.20 vs 0.14, $P < 0.001$; J: 0.38 vs 0.28, $P < 0.001$). There is increased temporal variation in J with respect to HS. These abnormalities of repolarization increase with worsening NYHA class, but do not correlate with ejection fraction.

Conclusions: The use of a universal correction formula to compare dynamic QT data in IHD patients is inappropriate. The observed progressive abnormalities may be responsible for the high incidence of sudden death through promotion of arrhythmias. **A.N.E. 2004;9(3):257–264**

QT; cardiomyopathy; repolarization; Holter

Congestive heart failure (CHF) is a common condition with high mortality. Many of these patients die suddenly,[1] and often tachyarrhythmias are responsible for this.[2,3] The failing ventricle exhibits prolongation of action potential duration (APD),[4] and prolongation of the surface QT interval is linked to malignant arrhythmias.[5–8]

To allow comparisons of QT interval data between individuals and populations, it is necessary to correct the QT duration for heart rate, as this is the greatest single influence upon QT. However, QT duration is also influenced by autonomic tone and the effects of many cardiac drugs. Correcting QT for rate is problematic and has led to the development of numerous linear, logarithmic, and exponential formulae, although researchers have questioned whether any single formula can be universally applicable.[9]

More recently, due to the developments in the field of electronics, it has become possible to analyze large quantities of data at high speed, with automated measurement of both the RR and QT intervals. This has enabled the study of long-term ECG recordings and assessment of the relationship between QT and RR. This has the advantage that large quantities of data can be processed quickly and removes some of the problems of interobserver errors in manual QT measurement.[10]

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re is also the advantage that assessment of repo-
ation over long recordings allows a more com-
e assessment of the relationship between QT
heart rate throughout the day, as considerable
adian variation in repolarization characteristics
ought to occur.[11–13] Unfortunately the analysis
ynamic recordings, where heart rate is varying
tantly, prompts special care when attempting
aw conclusions regarding short-term changes
e QT/RR relationship. QT does not adapt im-
iately to changes in RR but tends to lag behind.
time lag has been shown in cellular and pac-
studies to have two components[14–16] with an
ediate rapid phase with a very short time con-
that acts over the first or second inter-beat in-
l. The second delayed component has a much
er time constant, estimated at 1 min or more,
h means that several minutes are required be-
full adaptation of QT to the new heart rate
ached. Estimation of the QT/RR relationship
short time periods will, therefore, be influ-
d by incomplete QT adaptation and errors in
ation of the QT/RR slope or rate-corrected QT
will occur.[17] Automated methods for analysis
e QT/RR relationship have circumvented this
em by only analyzing steady-state data when
rate has been constant within a narrow range
period of time. This permits assessment of
eady-state QT:RR characteristic, but removes
ta when heart rate is changing. Our primary
tive was to describe the QT/RR relationship
continuous 24-hour data in patients with left
icular impairment, and to establish whether
was a correlation between abnormalities in
elationship and the severity of the condition.

METHODS

ent Population and Data Acquisition

ents with ischemic heart disease and ei-
symptoms of heart failure or left ventricu-
pairment (or both) who had been stable on
c medications for at least 1 month were suit-
or inclusion in the study. Left ventricular ejec-
action was estimated by standard echocardio-
c, angiographic, or radionucleide methods.
ts on agents known to prolong the QT in-
were excluded. Patients with bundle branch
(BBB) or atrial fibrillation were excluded.
rom recordings in 41 patients from NYHA
s I–IV were compared with 15 age-matched
y volunteers. NYHA functional class was as-
sessed by a clinician blinded to the results of the ambulatory ECG data. For the purposes of subanalyses, patients were divided into four broad groups according to ejection fraction (<15%, 16–25%, 26–40%, >40%). The characteristics of patients and controls are shown in Table 1. Twenty-four-hour ambulatory ECG recordings were acquired with two-channel ambulatory ECG recorders using standard bipolar thoracic leads CM1 and CM5.

Dynamic QT/RR Measurements

The tapes were replayed on a Pathfinder Analyzer (Del Mar Reynolds Medical Ltd., Hertford England), which excluded ectopic complexes and those that were significantly distorted by artefact. The analyzer measured each QT interval and the preceding RR interval. T_{end} was measured using the slope method, whereby, the end of the T wave is determined as being the point at which the current slope of the T wave drops below a predetermined proportion of the maximum slope. The accuracy of QT interval measurement has been validated independently.[18] Twenty-four-hour files of RR and QT intervals were then processed on a personal computer using VERDA software (Del Mar Reynolds Medical Ltd.). The three-stage process has been described elsewhere[17,19] but is outlined below.

For any given change in RR, the change in QT is related to the slope of the QT/RR plot at that heart rate. If changes in RR were infinitely slow, the plot would describe the steady-state characteristic and the change in QT (ΔQT) due to a change in RR (ΔRR) would be given by the formula

$$\Delta QT = S.\Delta RR.$$

Table 1. Characteristics of Subjects

	Healthy Volunteers	IHD
Age	53 (6)	57 (14)
Sex	10 male, 5 female	35 male, 6 female
EF	NA	25% (14)
Mean heart rate (SD)	71 (6)	70 (11)
Beta blockers	NA	50%
ACE Inhibitors/AII antagonists	NA	90%
Diuretics	NA	90%
Digoxin	NA	5%
Class III agents	NA	0%

Data are expressed as means (SD), or as percentages; NA = not assessed.

However, for more physiological changes in RR, one must incorporate a model for the lag phenomenon. The change in QT comprises an immediate undelayed fraction described as

$\alpha(S \cdot \Delta RR)$

and the remainder as the fraction

$(1 - \alpha) \cdot (S \cdot \Delta RR)$,

which has suffered a single-pole lag with a time constant of τ seconds. In Laplace transform notation the lag function is thus

$$\Delta QT(s) = [\alpha + (1 - \alpha)/(1 + s\tau)] \cdot S \cdot \Delta RR(s).$$

This model was refined electronically by adjusting the time constants and applying this lag function to the RR signal to create RR', an identically lagging version of the RR signal. From analysis of recordings from normal individuals, it was found that α remains relatively constant throughout the 24-hour period, with a population range of 0.22 to 0.31 (mean 0.26 ± 0.02). When the proportion of the fast and slow components of the lag function are correctly adjusted, the QT/RR plot no longer has hysteresis loops but traces out a curve which is presumed to be the underlying steady-state characteristic (Fig. 1).

During analysis the operator can monitor the removal of "hysteresis loops" and manually adjust the lag-compensation algorithm if necessary by adjusting the proportion of α.

Technically, however, this is now a QT/RR' plot as the QT data are the same, but the RR data have been delayed by applying the lag function. As these "pseudo-steady-state" plots are not linear but curved, the relationship is estimated by fitting the data against a general exponential formula with an X/Y intercept at zero. The curve can be described in terms of two variables—the exponent J and QTo, which is the QT interval at RRo, a reference RR interval (chosen as 1000 ms for reasons of convention).

Secondly, throughout the analysis, the RR' and QT signals are cross-correlated within a moving 5-min time window that is scrolled through the 24-hour data. As long as the correlation between QT and RR' remains high (correlation coefficient $r > 0.8$), the slope (S) of the QT/RR plot around each successive (RR', QT) point is computed as the linear regression coefficient in the 5-min time window currently centered on that point. Thus a continuously updated measure of the slope of the QT/RR' characteristic curve is generated. If the mean 5-min correlation coefficient drops below 0.8, these data are automatically edited out and not used for the calculation of 24-hour mean values of QTo, S, and

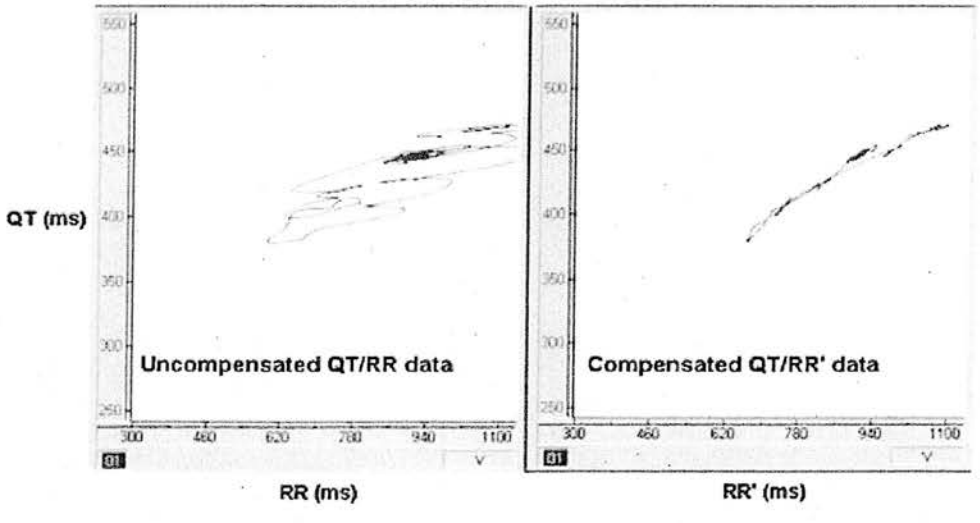

Figure 1. A 3-min excerpt of data as would be seen during analysis of a Holter recording. The panel on the left is a plot of raw QT values against the preceding RR intervals (QT/RR). Hysteresis loops are seen as heart rate accelerates and decelerates. The right-hand panel shows the same QT intervals plotted against the lag-compensated (RR') intervals. The resultant effect is seen as removal of the hysteresis loops, enabling the fitting of data to the exponential formula.

nlike some methods for QT/RR analysis, the are not divided into epochs, but rather, values ontinuously calculated from the mean of a con- ously scrolling 5-min window of data. Thus, if correlation coefficient transiently drops below nly data from this period are edited out, rather larger blocks of data. In this study, an average ± 4% and 93 ± 2% of 24-hour data was in- ed for analysis in the heart failure and healthy nteer groups, respectively.

irdly, it is found that the slope of the curve eases at longer RR intervals, providing evi- e that the steady-state QT/RR characteristic rved. To avoid the necessity of reporting the of RR at each measure of slope, a simple ic exponential formula, as adopted by both ricia[20] and Bazett[21] is used. These familiar for- e have given rise to some confusion regard- ne correct units for "QTc." To avoid this dif- y the present method uses the most general ssion:

$= QT/(RR/RRo)^J$.

QTo is the intercept of the curve with the or- e at RRo, a chosen reference RR interval (e.g., ms), and J is the exponent determining the of the curve (using Bazett's formula J = 0.5; idericia's, J = 0.33). The value of J is contin- y computed from J = S (RR'/QT), where RR' compensated value of RR.

overall 24-hour variation of J is expressed mean 24-hour standard deviation (SD) of J, derived from the mean of the continuously ated mean SD of J from the 5-min scrolling vindow.

Statistical Analysis

minimize the impact of noisy recordings on s, only tapes where the percentage of data an- was greater than 80% and the mean 24-hour ation between QT and RR' was greater than re included. Mean 24-hour parameters from recordings were compared between popula- y unpaired *t*-test.

RESULTS

re was no significant difference in mean 24- R or QT between the two groups. The mean r QTo was significantly prolonged in the roup (461 vs 426 ms, P < 0.005). The mean 24-hour slope (S) was also steeper in IHD (0.195 vs 0.140, P < 0.01). The mean 24-hour J (the exponent of the general formula that determines the form of the QT/RR curve) was significantly elevated in HF (0.38 vs 0.28). Constructed QT/RR curves created by using the mean population values of QTo and J are shown in Figure 2 to illustrate the different characteristics over a range of heart rates. In addition, the spread of values of J throughout the 24-hour period indicated by the mean 24-hour SD of J is much greater in the IHD group (0.181 vs 0.059, P < 0.01), reflecting an increased variation in the relationship between QT and heart rate. These data are summarized in Table 2. The increased variation in J cannot be explained by differences in the lag compensation as the overall correlation between QT and RR for compensated data is comparable

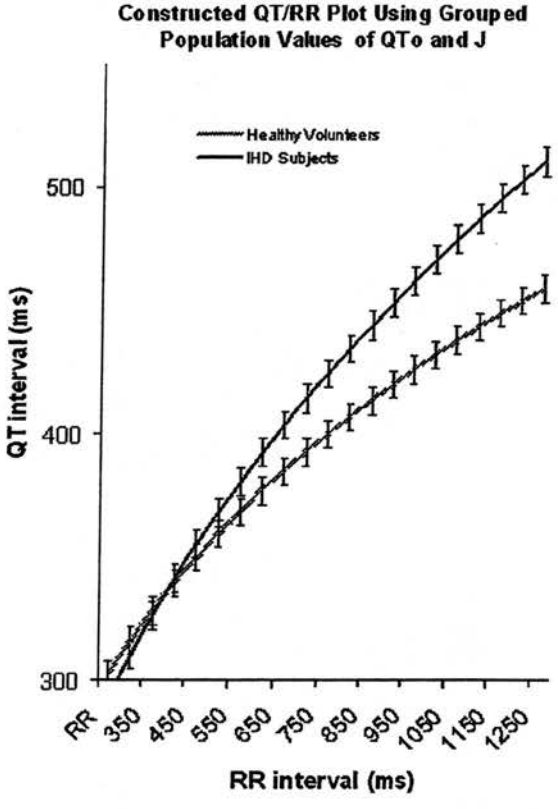

Figure 2. Curves generated from the mean population data in heart failure and healthy subjects. This illustrates how, at higher heart rates, little difference is observed between HF subjects and HV subjects. However, at lower heart rates, the combination of a higher J and longer QTo leads to a wider separation of the two curves. Error bars indicate standard errors of the means.

Table 2. Characteristics of 24-Hour Recordings

	RR (ms)	QT (ms)	QTo (ms)	S	J	24-Hour SD of J	Pooled 24-Hour Value
HV (n = 15)	845 (105)	402 (24)	426 (20)	0.14 (0.02)	0.28 (0.05)	0.05 (0.05)	0.742 (0.08)
IHD (n = 41)	859 (152)	420 (45)	461 (37)	0.20 (0.07)	0.38 (0.11)	0.181 (0.25)	0.77 (0.10)
P-value	0.76	0.18	<0.01	<0.01	<0.01	<0.01	0.25

Data are expressed as mean 24-hour values (SD).

between the two groups, as indicated by the similar-pooled mean 24-hour correlation (r).

When patients were subdivided according to NYHA class, the values of S, QTo and J increase with worsening functional class (Fig. 3). Analysis of variance (ANOVA) confirmed statistical significance (Table 3). In contrast, when patients were subgrouped according to ejection fraction (0–15%, 16–25%, 25–40%, and >40%), no significant difference is seen between the subgroups (Fig. 4).

CONCLUSIONS

The most appropriate method for assessment of ventricular repolarization is debatable. The simplest approach would be to take a resting 12-lead ECG and use one of the available correction formulae to correct for differences in heart rate. Unfortunately, the use of formulas to correct for heart rate are limited by the fact that most are only accurate at rest when heart rate is relatively low. In addition, they impose the same underlying QT/RR relationship on both populations, and can only be applied when heart rate has been stable for several minutes due to the significant time delay in reaching steady state. Investigators have shown that different subjects have different overall QT/RR relationships, and patient groups tend to have steeper QT/RR slopes and longer QT intervals, making direct comparison between populations using the same correction formula inappropriate. This is particularly true when using Holter data, which by nature are largely non-steady-state. The use of this method permits continuous assessment of the 24-hour relationship in patients with heart failure. Several differences come to light as a result.

Differences in the QT/RR Relationship between Heart Failure Subjects and Controls

When the overall QT/RR characteristic is examined, a marked difference emerges between patients and controls. The extrapolated QTo is significantly prolonged, and the exponent, J, is greater. The resultant effect of these two abnormalities is that the curves are separated over a broad range of heart rates, with the differences most marked at low heart rates.

The ability to detect prolongation of QT is dependent on the method used for correction of rate-related changes. Previous studies have shown that survivors of out-of-hospital cardiac arrests can have a normal QTc when traditional rate correction formulae are applied, but abnormal rate dependence when QT/RR plots are constructed with raw data.[22] This is an important point, because if one considers that in this study QTo is chosen arbitrarily as 1 s for no reason other than convention, it can be seen from Figure 3 that if QTo was set at, for example, 500 ms, little difference would be observed between the groups. QTo as a stand-alone measure of repolarization may show differences between populations, but when combined with the exponent J it takes on a much more useful role, as it allows description of the entire QT/RR characteristic, regardless of heart rate. Knowing both of these variables gives more precise information about repolarization at any point in time.

Increased Variability in the QT/RR Relationship

By calculating the mean 24-hour SD of J, information is obtained about the frequency and magnitude of changes occurring in the QT/RR characteristic throughout the day. In both healthy volunteers and HF variation is seen although the magnitude of this variation is greater in heart failure. This increased variation in the QT/RR relationship bears similarities with the work of Atiga et al.[23,24] They used a novel approach for the assessment of repolarization dynamics that assesses changes in QT with respect to changes in RR over relatively short time periods (256 s). When they compared healthy volunteers

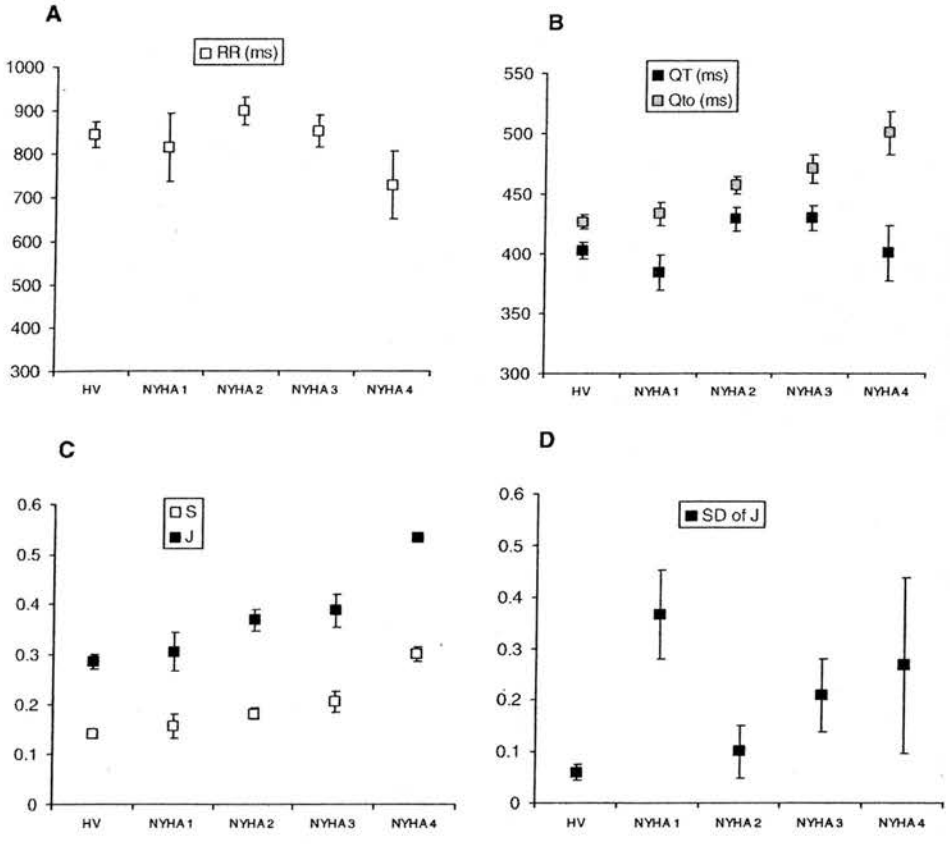

Figure 3. Comparison of the correlation between functional class, ejection fraction, and repolarization characteristics. Error bars indicate standard errors of the means.

patients, they found that there was decreased rate variance but an increase in QT variance patient groups. When these two parameters mbined to produce the QT variability index) they found that it discriminated between ntrol and patient groups. This increased vari- in the QT/RR relationship may reflect an in- of the myocardium to regulate repolarization anges in heart rate.

elation with NYHA Functional Class

ough this study was small, subjects were dis- ed across all four NYHA classes. When sub- were analyzed, it became apparent that the malities of the QT/RR relationship show a ning trend with functional class. NYHA func- class correlates with the degree of neuro- al activation in heart failure. The maladap- echanisms of increased sympathetic tone, sed parasympathetic activity, and activation of the renin-angiotensin-aldosterone system have been shown to, either directly or indirectly, influence cardiac repolarization, with downregulation of ion currents and abnormal expression of adrenergic receptors. These factors may be partly responsible for the progressive changes in repolarization

Table 3. Statistical Analysis of NYHA and EF Subgroups by Analysis of Variance (ANOVA)

	NYHA	EF
RR	0.17	<0.05
QT	0.11	0.09
QTo	<0.05	0.89
S	<0.005	0.66
J	<0.01	0.83
24-hour SD of J	0.11	0.59

In this table, P values are shown for each parameter measured, according to whether patients were subgrouped by NYHA class or ejection fraction.

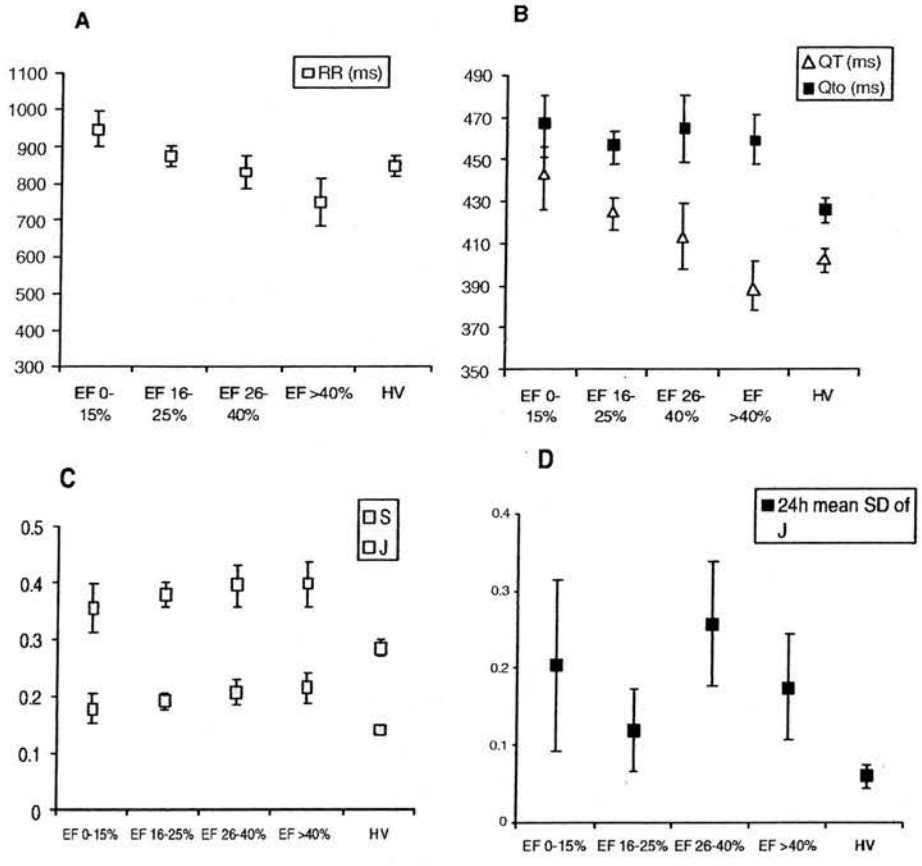

Figure 4. Comparison of the correlation between ejection fraction and repolarization characteristics. Error bars indicate standard errors of the means.

dynamics that we have described. Other investigators[25–27] have shown that beta-blockade reduces the slope of the QT/RR relationship in both healthy subjects and patients, and this implies that increased sympathetic drive is at least one of the factors responsible for the increases seen in J and QTo relative to controls.

Previous studies[28] have shown that sudden death is disproportionately common in relatively asymptomatic patients and our findings would seem to be discordant. However, arrhythmic death is frequently hard to determine as it is often unwitnessed and rhythms are not documented in the community. Certainly, patients with NYHA IV failure proportionately more likely to die from pump failure compared to NYHA I patients, but studies suggest that they are also very likely to die of arrhythmias.[3]

In summary, as both the "corrected" QT, and the exponent describing the curve (J) are different between controls and patients with LV impairment, the use of "off the shelf" rate correction formulas to correct QT for heart rate will lead to errors in measurement, particularly if used on dynamic data. The observed progression in QT prolongation, increased rate dependence, and increased variation in the relationship may promote ventricular arrhythmias and sudden death. Further studies will demonstrate whether prognostic information can be obtained using this method.

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